THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1960

ORIGINAL ARTICLES

PERSPECTIVES IN THE TREATMENT OF DIABETES*

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Progress frequently is associated with a sacrifice of simplicity. Therapy for diabetes is a good example. There is a wide variety of diets, each one of which has its advocates; there are eight insulins and a variety of mixtures of insulins to select from; and there are three oral preparations which may be employed singly or combined and with or without insulin.

The appropriate selections from these measures for the individual diabetic patient presuppose an understanding of diabetes in the broadest sense and of the properties of the drug or drugs selected. The failure to employ the optimal advantages at hand by partial treatment may be because authorities in this subject have not achieved their teaching objectives; the physician may never have had the opportunity of seeing diabetes well controlled and the gratifying results that ensue; or, it may be his doctrine that partial treatment is good enough. Alone or combined, these shortcomings encourage the progression of degenerative changes. It is not enough to make a severe diabetes appear mild or to secure adequate control for only a few hours out of each twenty-four. Partial treatment is better than none but surely it permits a harvest of tragedies.

It is because of the inferences indicated above that attempts have been made to put various measures in their appropriate perspectives and, in doing so, involve principles that could be put to good advantage in plans other than those outlined. Also, it is better that we should attempt to simplify therapy without restraint than to let the profession be infused with one-sided but nevertheless simple plans born of commercial interests.

THE DIET. TOTAL CALORIES. Reduction of the total caloric intake sufficient to reduce the overweight is desirable. This effective measure will suffice to control the diabetes, barring acute complications, in the majority of diabetic patients.

For the overweight patient having no acute complications, one has the choice of supplementing undernutrition with a sulfonylurea compound.

*Presented, with minor alterations, before the American Clinical and Climatological Association, Hot Springs, Va., Nov. 3, 1959.

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The patient develops the proper perspective, however, if success is achieved by diet alone. Otherwise, the diet becomes secondary in importance to drug therapy. If the attractive temptation to substitute drug therapy for undernutrition is adopted, glycosuria is corrected and the obese state is intensified as a result. Is this better or worse than allowing glycosuria to neutralize the surplus dietary intake and by doing so encourage the progression of degenerative changes? Both schemes represent clinical failures. There is no legitimate substitute for the reduction of the obese diabetic.

Carbohydrate. The carbohydrate is necessarily reduced in the undernutrition regimen. For diabetics who are normal or under normal in weight and who are receiving liberal diets, we have steadily increased the carbohydrate allowances until they are as close as is practicable to that in the diet for the normal individual without appreciably increasing the difficulty in controlling the diabetes. Quotas as high as 250 gm., or more, are common. satisfactory blood sugar levels around the clock are obtained in most cases with such allowances when appropriate insulin therapy and distribution of the diet are maintained. In the final analysis, it is the total calories and not the carbohydrate that exerts the greatest effect on the need for insulin (Allen[1]).

The liberalizing of the carbohydrate permits less fat. One wonders how much the relatively high fat content of diets for diabetics has contributed to the progression of atherosclerosis. I am convinced that it has had this effect, hence we allow more liberal amounts of protein and carbohydrate in diets for our patients than is generally employed or was formerly the case in our own practice. The subsidence of anginal attacks in the atherosclerotic diabetic with an elevated serum cholesterol when the fat content of the diet is low and when it is provided, for the most part, in the unsaturated form is sufficiently frequent to warrant an exploratory long-term application of this regimen. The beneficial effect in cases of diabetic retinitis when the fat content is reduced to 20 gm. per day is an added stimulus to give this plan of diet therapy in such cases an adequate trial (Van Eck[6]).

INSULIN THERAPY. Plans of insulin therapy which have stood the test of time and comparative studies are:

(A) A single dose of an intermediate-acting insulin (Globin, NPH or Lente) given one hour before breakfast. Employed for relatively mild cases, in which the subjects are not overweight, this regimen, when adequate, has been largely replaced by oral therapy.

(B) A mixture of a rapidly acting and an intermediate-acting insulin, notably NPH (Isophane) insulin, given before breakfast, is used when an intermediate acting insulin fails to prevent hyperglycemia during the forenoon. Some of these patients achieve good control with tolbutamide or chlorpropamide without insulin.

(C) For the juvenile type of diabetes characterized by marked lability of the blood sugar, an additional small evening dose, after supper, of an intermediate-acting insulin is necessary to avoid nocturnal hyperglycemia. This dose is usually given after, but in some case before, supper, and in others at bedtime. None of my patients who has needed this plan of insulin therapy has been able to substitute oral therapy for it. A small percentage achieve adequate control with a mixture of 2:1 or 3:1 of crystalline and protamine zinc insulins. Beyond this occasional use, there is no apparent need for protamine zinc insulin in the therapy for diabetes.

(D) Crystalline insulin has a quicker

blood sugar lowering effect than semilente insulin and hence is the insulin of choice in the early management of the ketotic patient. Either of the rapidly acting insulins, crystalline or semilente, is well suited for the management of diabetes during acute complications when the diet is divided into four equal feedings given at 6-hour intervals (Duncan, Fetter and Durkin[2]).

a normal nutritional state, none of these patients is a candidate for oral therapy. To these can be added at least an additional 5%, the juvenile diabetics, and another 5% who are adults but who have a juvenile type of diabetes in whom the sulfonylureas are ineffective. There remains 10% who are "ideal" candidates for sulfonylurea therapy. These patients are not overweight and have an adult-acquired stable type of

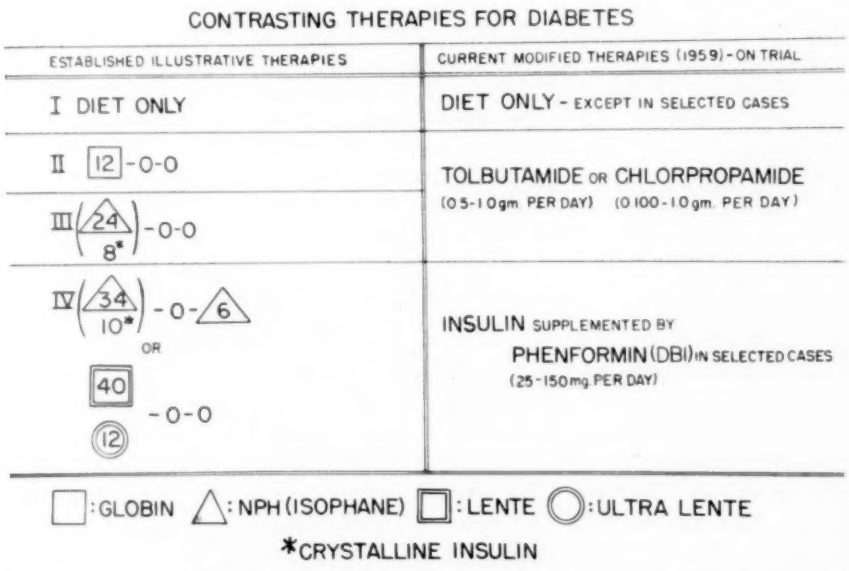

Fig. 1.—The current influences of oral drug therapy for diabetes mellitus are contrasted with established, illustrative plans of insulin therapy.

All insulins are effective in reducing the blood sugar, and while various combinations and mixtures may serve well, we have found that the foregoing plans of therapy, as illustrated in Fig. 1, give the most predictable results.

ORAL THERAPY. Oral drug therapy *idealistically* has a small field of usefulness in the treatment of diabetes. Realistically the opposite is the case. If we agree that 80% of the diabetic population is sufficiently overweight to allow control of the diabetes by restoring

diabetes. They cannot afford to lose weight but either tolbutamide or chlorpropamide may be satisfactorily effective in at least 75%. Though this is the ideal group for sulfonylurea therapy, it is in this group that most of our secondary failures occur. It should be said, however, that the diabetes in some of these cases has been more easily and better controlled with a sulfonylurea than with insulin.

Phenformin, it would appear, has its greatest promise, not in treating the

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patient with mild diabetes, but in reducing the need for insulin and exerting a stabilizing effect on the juvenile type of diabetes.

Sulfonylurea compounds: (A) Tolbutamide is the drug of choice *if* good control of the diabetes is achieved with it. Side effects are rare if the daily dosage does not exceed 1 gm. Half a gram of tolbutamide given before breakfast may suffice. If more is needed, the same amount is given before lunch. These 2 doses exert their maximum blood sugar lowering effect during that period of the 24 hours when 3 meals are consumed in relatively close succession, and this effect is on the wane during the night when no food is taken.

(B) Chlorpropamide. Unlike tolbutamide, a blood sugar lowering concentration of chlorpropamide in the blood is maintained throughout the 24 hours by the administration of one dose per day. Also, it is significantly more potent than tolbutamide in its blood sugar lowering effect. Because of these features, hypoglycemic episodes may occur between midnight and breakfast, hence the need of giving a bedtime nourishment. The maintenance daily dose of chlorpropamide varies from 0.25 to 1.0 gm. Half a gram is the amount most frequently used.

These two sulfonylurea compounds are ineffective in the juvenile diabetic or in the adult who shows prompt and increasing amounts of acetone in the urine when the amount of insulin given is appreciably reduced. Furthermore, they are ineffective during febrile episodes and infections. Whether or not these drugs will serve as effective supplements to insulin therapy in the "juvenile type" of diabetes is not definitely established, though Fabrykant[4] and others make this claim for them. This effect might be expected, as Houssay *et al.*[5] have shown that the sulfonylureas appear to potentiate the action of injected insulin in eviscerated animals. Our results with reliable patients and with the diabetes under satisfactory control have not supported Fabrykant's observations. When apparent benefit was noted, it appeared to be attributable to increased attention to the diet, by the less reliable patients, during the studies.

An appreciable reduction in the amount of insulin needed has, however, been noted in our experience (Duncan, Joiner and Lee[3]), in the very occasional patient who is normal in weight or is underweight, has a labile diabetes, and requires unusually large amounts of insulin, between 100 and 200 units. This result is exceptional. These rare patients violate the usual rule in that they develop ketosis readily with a considerable reduction in the insulin dosage, and yet the sulfonylurea has a moderately favorable effect on the insulin requirement but not to the degree which would allow its omission. The relative places of the three oral preparations in the treatment of diabetes in its various grades of severity are indicated in Fig. 2.

Phenformin (DBI) is a blood sugar lowering biguanide effective in severe and labile as well as mild adult acquired diabetes. However, because of the high incidence of nausea and vomiting complicating its use (20 to 50%), it appears wise to restrict its use to the patients with labile diabetes, that is, to those who are deprived of the benefit that could otherwise be obtained by an undernutrition regimen or a sulfonylurea compound. Fewer gastrointestinal disturbances occur if the initial dosage of Phenformin is small, 12.5 mg. with each meal. Increases by increments of 12.5 mg. are made at 2- or 3-day intervals with reductions

in the amounts of insulin given if this is indicated. The daily total of Phenformin should not exceed 150 mg. and frequently gastrointestinal disturbances will dictate considerably less.

Summary. There is no substitute for diet therapy in the treatment for diabetes. Claims that more than one-half of the known diabetics in this country are receiving tolbutamide suggest a administration is the most effective anti-diabetic agent known.

Oral therapy is a treatment of convenience and not of necessity. The sulfonylureas are most effective, numerically, in those patients whose diabetes can be controlled without drug therapy. They have, however, a justified place in the management of approximately 10% of diabetic patients. They are effec-

CURRENT PERSPECTIVES IN ORAL THERAPY FOR DIABETES (1959)

CHARACTERISTICS	REDUCING DIET	TOLBUTAMIDE (ORINASE)	CHLORPROPAMIDE (DIABINESE)	PHENFORMIN (DBI) SUPPLEMENTING INSULIN THERAPY
A OVERWEIGHT PATIENT WITH ADULT ACQUIRED STABLE DIABETES RESISTANT TO KETOSIS	*	* (IN SELECTED CASES)		
B NEAR NORMAL WEIGHT ADULT ACQUIRED STABLE DIABETES RESISTANT TO KETOSIS		*		
C SAME AS B BUT NOT CONTROLLED BY TOLBUTAMIDE			*	
D LABILE DIABETES IN ADULT AND JUVENILE PATIENTS		?	?	*

Fig. 2.—Diet therapy, alone or with oral therapy, tolbutamide, chlorpropamide and Phenformin are shown in conservative perspectives as related to the various grades of severity of diabetes.

gross violation of this conservative truism.

More liberal quotas of protein and carbohydrate are indicated as a practical means of reducing the fat content of the diets. This seems to be especially desirable for the atherosclerotic patient with hypercholesterolemia. Also, in these cases benefit accrues when the fat is provided in a high proportion of unsaturated forms.

Insulin in one form or another or in suitable combinations and timing of

tive supplements in the treatment of the overweight diabetic but the likelihood that such effective agents might receive widespread adoption as a substitute for appropriate dietary measures must be guarded against. Failing in this would, and apparently does, mean that diabetes in this preponderant group of overweight subjects is not being as well treated, in the overall picture, as it was before these drugs were available.

Phenformin is a potent blood sugar

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lowering agent and may prove to be of long term value in the management of the juvenile type of diabetes. This has not yet been established. Phenformin is not considered a suitable substitute for sulfonylurea compounds in cases in which they are satisfactorily effective.

The optimum therapy for diabetes depends upon diet, insulin and oral preparations being kept in their proper perspectives.

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SUMMARIO IN INTERLINGUA

Perspectivas in le Tractamento de Diabete

Nihil pote prender le placia de therapia dietari in diabete. Assertiones que plus que un medietate del cognoscite diabeticos in le Statos Unite recipe tolbutamido suggere un grossier violation de iste veritate trivial.

Quotas plus liberal de proteina e hydrato de carbon es indicate como mesura practic pro reducer le contento de grassia del dietas. Isto pare esser specialmente desirabile in le caso de patientes atherosclerotic con hypercholesterolemia. In plus, in iste mesme casos le patientes beneficia si un alte proportion del grassia es providite in formas non-saturate.

Insulina in un forma o un altere o insulina in appropriate combinationes con appropriate horarios de administration es le plus efficace agente anti-diabetic que es cognoscite.

Le therapia oral es un tractamento de convenibilitate e non de necessitate. Le sulfonylureas es le plus efficace—numericamente—in patientes cuje diabete pote esser bridate sin therapia a drogas. Tamen, le sufonylureas ha un rolo justificabile in le tractamento de approximativemente 10 pro cento del patientes con diabete. Illos es efficace supplementos in le tractamento del diabetico obese, sed le possibilitate que tal agentes es extensemente adoptate como reimplaciamento de appropriate mesuras dietari debe esser reguardate como un periculo. Alteremente le resultato esserea (e de facto es) que diabete in le grande gruppo de subjectos qui es obese es tractate minus efficacemente—a generalmente parlar—qué ante le advento de iste drogas.

Phenformina es un potente agente pro le reduction del sucro del sanguine. Il es possibile que illo va provar se de valor a longe vista in le tractamento del typo juvenil de diabete. Isto ha non ancora essite establite como un facto. Phenformina non es considerate como un appropriate substituto pro le compositos de sulfonylurea in le casos in que iste ultimes es satisfacentemente efficace.

Le therapia optime pro diabete depende del dieta, del uso de insulina, e del utilisation de preparatos oral in un perspectiva salubre.

PREVENTION OF RECURRENT RHEUMATIC FEVER IN CHILDREN AND ADULTS WITH ORAL AND REPOSITORY PENICILLIN*

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The effectiveness of antibiotic prophylaxis in preventing recurrences of acute rheumatic fever by diminishing the risk of acquiring new Group A streptococcal infections has been demonstrated in a number of military and civilian studies (Denny[2], Mortimer and Rammelkamp[14], Tidwell[19], Wannamaker *et al.*[20], Wood[21]). Variations in dosage and route of administration have been investigated by several investigators (Diehl *et al.*[3], Massell *et al.*[11], McCue, Gibson and Lindemann[12], Stollerman, Rusoff and Hirschfeld[18], Wood *et al.*[22]).

The value of repository (benzathine) penicillin as a prophylactic for streptococcal infections was reported first by Stollerman and Rusoff[17] and subsequently confirmed by others (Chamovitz *et al.*[1], Diehl *et al.*[3], Lade *et al.*[9], Massell[10], McCue, Gibson and Lindemann[12]). Stollerman found that detectable penicillin blood levels were present for as long as 3 to 4 weeks after a single injection of 1,200,000 units of benzathine penicillin. Adverse systemic reactions were no problem. The repository salt had one major point of superiority in that it made certain that the patient had received his medication.

While prophylaxis programs generally are of the continuous type, Kohn, Milzer and MacLean[8] used intermittent prophylaxis in which therapeutic amounts of penicillin were administered orally during the first week of the month, except during January, February and March when treatment was provided for an additional week in the middle of the month. This method has not achieved very broad acceptance.

Little of the available data on the prevention of recurrent rheumatic fever deals with adult populations. Since the disease may follow any streptococcal infection and since this may occur any time the host comes in contact with an organism to which he is not immune, it is our belief that protection should be provided for life, for adults as well as children.

The study which forms the basis of this report was initiated to obtain additional information on the comparative effectiveness, acceptability and

*Supported by grants from Wyeth Laboratories, Inc., the Onondaga Health Association, the Heart Association of Onondaga County, the Masonic Foundation for Medical Research and Human Welfare and F. K. Kilian.

toxicity of oral and repository penicillin both in children and adults.

Material and Methods. This report is based upon the first 3 years of experience of a rheumatic fever prophylaxis clinic which was organized in 1955. The patients were admitted to the clinic only if they had rheumatic heart disease or if the staff accepted the diagnosis of previous acute rheumatic fever. They were referred from a number of sources: private physicians, general hospitals in the area, the Syracuse Dispensary and the Wieting-Johnson Hospital for Rheumatic Diseases. At the first visit, a detailed history was obtained, the patient examined and assigned to either the oral or repository group by alternation. Clinic sessions were held on one of four Tuesdays of the month, each patient attending on the same relative day of the month. Occasionally the Dispensary was closed on a Tuesday, resulting in an interval between clinic visits of as short as 21 or as long as 35 days. This was compensated for in the oral group by increasing or decreasing their tablet supply but no attempt was made to adjust the injected material.

A throat culture and blood specimen* (for sedimentation rate, hematocrit, C-reactive protein and antistreptolysin-O determinations) were procured at the initial, and subsequently, at each monthly visit. An electrocardiogram and roentgenological study of the heart were obtained at the first visit and annually thereafter.

If the patient failed to keep his appointment, a reminder postcard was mailed immediately. If 3 consecutive appointments were missed, a nurse was asked to review the problem in the patient's home.

Patients in the oral group were provided with a 200,000 u tablet of benzathine penicillin G† (Dibenzylethylenediamine dipenicillin G) to be taken each morning. The alternates received an intramuscular injection of 900,000 units of benzathine penicillin G once a month. Patients with a history of penicillin hypersensitivity and those who developed such allergy during the observation period were maintained on daily 0.5 gm. doses of sulfamethoxypyridazine‡ (Kynex).

At each follow-up visit the patient was questioned whether, in the intervening period, acute respiratory illness or sore throat had occurred in himself or his family and whether he had had a rash, epistaxis, joint pains or swelling. Inquiry was made regarding the regularity with which he had taken the prescribed oral medication and whether he had had any reaction to his medication. If he insisted, he was transferred to another treatment regimen and his reasons noted. Cardiac auscultation and whatever other examinations were indicated, were performed at monthly or bi-monthly intervals.

Altogether 139 persons were observed for a total of 1,978 patient months. Females comprised 60% of the population; the age spread was from 8 to 74 years with 28% less than 20 years old (Table 1). As a sign of the times, 5 patients had recovered from subacute bacterial endocarditis and 10 had had previous cardiac surgery. These 15 patients represent 11% of the clinic's population.

The racial composition of the clinic was: Caucasian 115, Negro 19, Indian 3 and undefined 3. Females predominated in each racial group and more were admitted in all decades, except the second.

While a definite history of rheumatic fever in one of their parents was elicited from 9% of the patients, 20% indicated that at least one of their siblings had had rheumatic fever.

The functional cardiac status[15] of each patient was determined at the time of his admission to the clinic; more than two-thirds (96 patients) were in Class I, one-quarter (35 patients) in Class II, and 6% (8 patients) in Class III (Table 2). There were no Class IV patients because of the nature of the clinic.

*Throat swabs were plated directly on sheeps blood agar and again after incubation in modified Pike's broth (Feldman and Harmon[6]). Sedimentation rates and hematocrits were measured in Wintrobe tubes by a standardized technique. C-reactive protein determinations were made with either Schieffelin or Difco antisera. Antistreptolysin-O was titrated by a method in use in this laboratory (Gillen, A. L. and Feldman, H.A. Unpublished.) which uses sheep erythrocytes. Hemolysis is measured spectrophotometrically and the method is sensitive and highly reproducible. The reporting system is in units about five times larger than the standard Todd unit. For example, a titer of 1500 units in our system is approximately equivalent to 300 in Todd units.

†We are indebted to Dr. Edward F. Roberts, Wyeth Laboratories, Philadelphia, Pennsylvania for the two forms of Bicillin used throughout this study.

‡The Kynex was kindly supplied by Dr. Stanton M. Hardy, Lederle Laboratories, Pearl River, New York.

TABLE 1.—CHARACTERISTICS OF RHEUMATIC FEVER PROPHYLAXIS CLINIC POPULATION

		Male		*Female*		*Totals*	
Characteristics		*No.*	*%*	*No.*	*%*	*No.*	*%*
Age (*yrs.*)	<20	21	54	18	46	39	28
	20+	34	34	66	66	100	72
	Totals	55	40	84	60	139	100
Race	White	47	41	68	59	115	83
	Negro	7	37	12	63	19	14
	Indian	1	33	2	67	3	2
	Unknown	1	50	1	50	2	1
Other	Had SBE	3	60	2	40	5	100
	Had Card. Surg.	4	40	6	60	10	100

TABLE 2.—FUNCTIONAL° CARDIAC STATUS WHEN ADMITTED TO CLINIC

	Treatment Group							
	Pen. p.o.		*Pen i.m.*		*Sulfa*		*Totals*	
Class	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	54	73	41	68	1	20	96	69
II	17	23	14	23	4	80	35	25
III	3	4	5	9	0	0	8	6
Totals	74	100	60	100	5	100	139	100

°(15)

The occurrence of congestive heart failure prior to admission to the clinic is summarized in Table 3. Among the 37 persons who were less than 20 years old on admission, 2 (5%) had had an episode of congestive failure. Fifteen (25%) of the 61 persons in the 20 to 39 year age group and 11 (31%) of the 35 patients 40 years or older when admitted to the clinic had had at least one episode of congestive failure. Such information was not obtainable from 6 patients who were excluded from this analysis. Of those who had been in congestive failure more than once, one was less than 20 years of age, 3 were between 20 and 39 years and 8 were over 40.

The age at the time of the initial attack of rheumatic fever (Table 4) was reported to have been less than 15 years by 79 (71%) patients, between 15 and 39 years by 30 (27%) and after age 40 by 2 (1%). The age of onset was the same in both males and females.

Of the 134 patients from whom such a history was obtainable, 39 (29%) had had more than one episode of acute rheumatic

TABLE 3.—OCCURRENCE OF CONGESTIVE FAILURE (BY HISTORY) PRIOR TO ADMISSION TO CLINIC

	Heart Failure		*No Heart Failure*		*Totals*	
Age (Yrs.)	*No.*	*%*	*No.*	*%*	*No.*	*%*
<20	2	5	35	95	37	28
20–39	15	25	46	75	61	46
40+	11	31	24	69	35	26
Totals	28	21	105	79	133	100

fever prior to entering the clinic (Table 5). A single attack was reported by 95 (71%) but 13 (10%) had had 3 or more. Of the 29 patients who withdrew, 23 (79%) had had one attack, 4 (14%) two and 2 (7%) four attacks of rheumatic fever.

Replies to questions about the treatment of their first attack of rheumatic fever were obtained from 92 patients. Twenty-four (26%) could recall no special treatment but 41 (45%) had been placed on bed rest for varying periods of time. Sixteen patients (17%) reported having received salicylates during the acute phase of their illness and 10 (11%) remembered being treated with steroids or steroids plus salicylates during this stage. One patient (1%) stated that he had been treated with digitalis during his acute illness. A greater proportion of the patients under 20 years, 18% (6) received steroid therapy as compared to those over 20 years, 3% (1). Only 5 (15%) of the patients under 20 years of age had not received specific treatment compared with 19 (32%) of those more than 20 years of age.

Forty-three of 135 (32%) patients had been hospitalized on one occasion for rheumatic fever; 15 (11%) had had 2 or more hospitalizations but 77 (57%) never were hospitalized for this reason.

Five (13%) of the patients under 20 years of age, 19 (31%) of those between 20 and 39 years and 18 (49%) of those over age 40 had been hospitalized for complications of rheumatic heart disease.

The interval between acute rheumatic fever and the institution of some form of prophylaxis varied with age. Among 33 patients less than 20 years old, 24 (73%) had been started on prophylaxis within 2 years of their acute episode (Table 6). This was true for only 15 (19%) of the 79 persons 20 years or older. Eight (24%) of those less than 20 years of age received their initial prophylaxis 6 or more years after an attack; 59 (75%) of those over 20 were started after a similar interval.

Of the 139 persons, 112 (80%) had received some kind of prophylaxis prior to entering the clinic (Table 7) but in many instances this was limited to the period between referral from other clinics to this one. Penicillin, uniformly the commonest drug employed in all age groups, had been used by 75% of the patients. Sulfonamides had been used by only 4% and 1% had had both penicillin and sulfonamide. Among the 27 persons (20%) who had not received any prophylactic medication, slightly more were in the age group above 40 years.

Admission information regarding allergic manifestations to prophylactic agents was obtained from 137 patients; 115 (84%) denied having had reactions to either penicillin or sulfonamides. Of the remainder, 12 (9%), said that they had reacted to penicillin and 7 (5%) to sulfonamides.

TABLE 4.—AGE (BY HISTORY) AT FIRST ATTACK OF ACUTE RHEUMATIC FEVER IN CLINIC POPULATION

Age (Yrs.)	Male		Female		Totals	
	No.	%	No.	%	No.	%
<15	33	75	46	69	79	71
15–39	11	25	19	28	30	27
40+	0	0	2	3	2	2
Totals	44	40	67	60	111	100

TABLE 5—NUMBER OF ATTACKS (BY HISTORY) OF ACUTE RHEUMATIC FEVER PREVIOUS TO ENTERING PROPHYLAXIS CLINIC

No. of Attacks	Male		Female		Totals	
	No.	%	No.	%	No.	%
1	39	72	56	70	95	71
2	11	20	15	19	26	19
3	1	2	6	7	7	5
4	0	0	2	3	2	2
5	3	6	0	0	3	2
6	0	0	1	1	1	1
Totals	54	40	80	60	134	100

TABLE 6.—INTERVAL BETWEEN LAST EPISODE OF ACUTE RHEUMATIC FEVER AND INSTITUTION OF CHEMOPROPHYLAXIS

Interval (Mos.)	Age Group (Yrs.)				Totals	
	<20		20+			
	No.	%	No.	%	No.	%
6 or <	15	46	10	13	25	22
7–24	9	27	5	6	14	13
25–48	1	3	2	3	3	3
49–72	0	0	3	4	3	3
73+	8	24	59	75	67	60
Totals	33	30	79	70	112	100

Results. The 78 persons who received penicillin orally accumulated 932 patient-months of experience, the 74 on the intramuscular regimen had 977 patient-months and the 5 on sulfamethoxypyridazine had 69 patient months (Table 8). Although assignment to the oral and intramuscular penicillin groups was by alternation, the former had more females than males but the reverse was true for the latter.

Seven of the 12 patients (58%) who requested a change from intramuscular to oral penicillin eventually left the clinic. Conversely, both patients who asked to be transferred from oral to intramuscular medication, remained in the clinic. The reason was the same in each instance, namely, difficulty in remembering to take the pills.

When interviewed each month, patients were asked whether they had taken their oral medication each day. Thirty-eight (52%) said that they took it regularly, 16 (22%) rarely missed a dose and 19 (26%) frequently forgot their penicillin. Those under age 20 had the best record for only 3 (13%) failed to take their tablets frequently

TABLE 7.—RHEUMATIC FEVER CHEMOPROPHYLAXIS RECEIVED PRIOR TO ADMISSION TO CLINIC

Age (Yrs.)	*Penicillin*		*Sulfa*		*Pen. + Sulfa*		*None*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
<20	31	79	1	3	0	0	7	18
20–39	47	76	4	6	2	3	9	15
40+	26	68	1	3	0	0	11	29
Totals	104	75	6	4	2	1	27	20

TABLE 8.—PROPHYLAXIS EXPERIENCES OF 139* RHEUMATIC FEVER CLINIC PATIENTS

Treatment Method	*Male*		*Female*		*Totals*		*Patient-Months of Observation*
	No.	*%*	*No.*	*%*	*No.*	*%*	
Penicillin p.o.	24	39	54	56	78	50	932
Penicillin i.m.	35	58	39	41	74	47	977
Sulfamethoxypyridazine	2	3	3	3	5	3	69
Totals	61	100	96	100	157†	100	1978

*37 of 139 (26.6%) patients withdrew from the program.
†Treatment changes a) penicillin p.o. to i.m. 2
b) " i.m. to p.o. 12
c) " p.o. to sulfamethoxypyridazine 2
d) " i.m. to " 1

The major objective in effective rheumatic fever prophylaxis is to provide for the preventive medication to be received consistently. Of the 139 persons admitted to the clinic, 37 (27%) were lost during this initial 3-year period. Of these, 8 moved to other communities, one died and the remaining 28 (22%) failed to maintain attendance. The latter did not return after either a postcard or a visit by a nurse. Two (14%) of the 14 patients on intramuscu-

and 15 (63%) presumably maintained a regular intake.

Fifty-three patients were questioned about their most recent experiences with repository penicillin. Nine (16%) reported minimal to mild pain at the injection site persisting for one day, 12 (23%) for 2 days, 5 (9%) for 3 days, and 3 (6%) for 4 days; 24 (46%) had had no significant pain. Among 46 of these patients who were questioned as to their preference for oral or intramuscular medication, 26 (57%) preferred the latter, 13 (28%) didn't care and 7 (15%) would have preferred oral therapy had they been given a choice.

During the three years of this report period, Group A streptococci were isolated three times from 2,247 cultures. Two of the positive cultures were obtained at initial visits, prior to the institution of prophylaxis. The third culture occurred in a patient who had failed to keep his clinic appointment one month earlier.

Group B streptococci were detected three times, twice from the same patient. Group C streptococci were isolated twice, once in the patient who had had the 2 Group B cultures. A non-groupable beta hemolytic streptococcus was isolated once from another patient. There was no history of an acute illness that could be related to the Group B, C and non-groupable streptococcal demonstrations. Two of the Group B and one of the Group C isolations were accompanied by increases of more than 20% in the appropriate antistreptolysin-O (AS-O) titer*. Three patients on oral penicillin had AS-O increases that approximated the isolation of either Group B or Group C streptococci.

There were 23 instances of AS-O increase (13, oral penicillin, 10, intramuscular) in patients who had failed to receive penicillin for a month or more. Among patients receiving repository penicillin regularly, significant AS-O rises were noted 30 times. The same was true for 22 patients who we are reasonably certain took their oral medication.

The AS-O data from the 3 treatment groups have been combined in Fig. 1. Since no major quantitative differences were noted in relation to age or sex, these variables have been omitted from the figure. It will be noted that there has been a progressive fall in the median AS-O value for the entire clinic population, from a high of 1750 to 800 units at the time of analysis. This is especially noteworthy since new patients were added to the sample as they were inducted into the clinic. Some had high titers because they had recovered recently from acute rheumatic fever. This decline is even more strikingly illustrated in Fig. 2. The 42 patients who were admitted to the clinic with initial AS-O titers of 2000 or more were selected for this analysis. The initial median AS-O titer for the females was 3200 units and for the males, 3300 units. The median value for females decreased to 1000 units in slightly less than 3 years. Among the males a median value of 800 units was noted in 2 years.

When the AS-O data were analyzed in specific groups of patients, it was noted that slight rises in the median titers were uniformly detected between October and April. Quantitatively, the increases in the median titers were greater in females, occurred in all three age groups and regardless of treatment except for those between 20 and 39 years on intramuscular penicillin. The male patients exhibited a median AS-O rise either on oral or intramuscular

*The method employed is reproducible within limits of ± 10%.

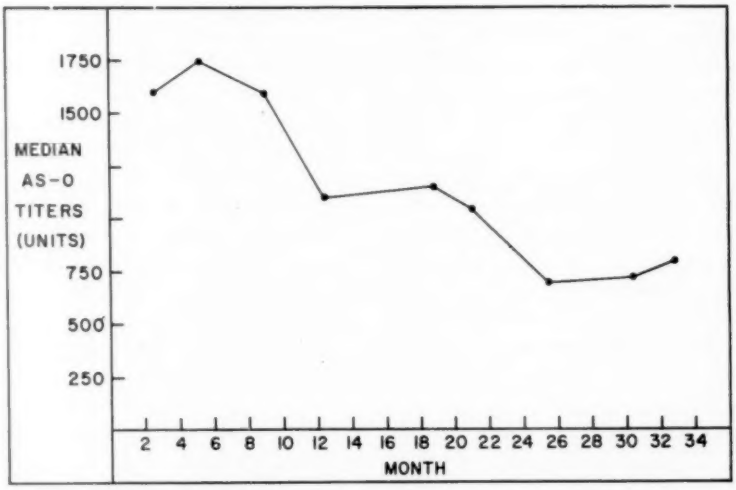
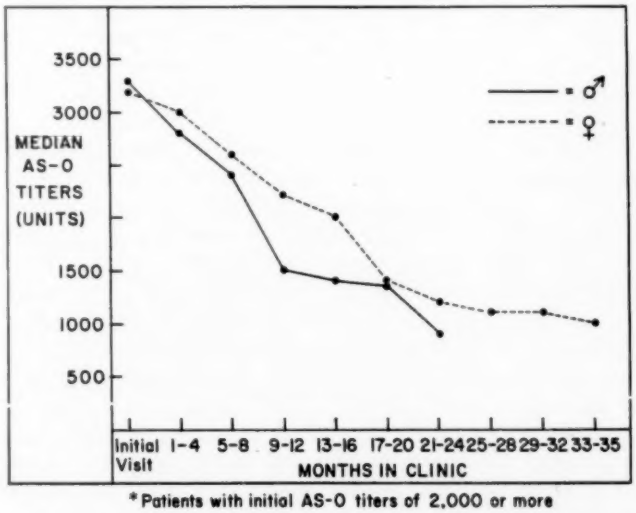


Fig. 1.—Changes in median antistreptolysin-O titers of 139 patients during rheumatic fever prophylaxis.



*Patients with initial AS-O titers of 2,000 or more

Fig. 2.—Changes in median antistreptolysin-O titers of 42 patients* during rheumatic fever prophylaxis.

penicillin in the age group 20 to 39 years. The median titers of male patients under 20 and over 40 years did not increase.

It is difficult to correlate the results of the 2 laboratory tests used to detect the presence of inflammatory reactions, namely the C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR). Since chemoprophylaxis is designed to prevent streptococcal infections, one would expect the AS-O titer changes to be considerably less frequent than those for the CRP and ESR. Among the 139 patients, 65 (47%) were free of significant AS-O increases, and 71 (51%) had no instances of CRP activity. On the other hand, only 30 patients (22%) did not have an abnormal ESR at some time during their clinic attendance.

Twelve patients (9%) had neither an AS-O elevation nor a CRP or ESR abnormality at any time. These were all patients who had attended the clinic for 18 months or less. There were 15 patients (11%) who had neither AS-O nor ESR changes, but there were 40 patients (29%) with neither AS-O nor CRP abnormalities.

We were unable to correlate AS-O increase with positive CRP reactions in chronological terms. In 71 instances in which an AS-O increase of greater than 20% was noted, the CRP reaction was positive 12 times (17%), reflecting, perhaps, the transient character of the CRP reaction. The routine performance of CRP or ESR tests in patients who are followed at monthly intervals in a clinic of this kind appears to be of questionable value.

It was not possible to relate AS-O elevations to regularity of clinic attendance. For example, among 60 patients who kept more than 80% of their appointments, there were 21 instances of AS-O increases in excess of 20% (one patient had such an increase in each of 2 successive years). On the other hand, 15 patients who kept fewer than 60% of their appointments had AS-O increases on 4 occasions.

An attempt was made to relate the occurrence of throat symptoms to AS-O rises. Among 21 patients with such an elevation who kept more than 80% of their appointments, 10 had no throat symptoms but 11 had such complaints either in the month preceding or in the month of the AS-O rise. Of the 16 patients who had AS-O increases and who attended less than 80% of the time, 12 had no pharyngeal complaints but 4 had symptoms in the same or previous month. Thus, of 37 patients, 15 had throat symptoms that might have been related to their serological changes but 22 had not had throat symptoms in the related period.

When admitted to the clinic, 115 (83%) patients denied having had any previous allergic reactions to either penicillin or sulfonamides. One individual less than 20 years of age gave a history of having had a rash following sulfonamide but 23 persons older than 20 years said that they had previous sulfonamide or penicillin sensitivity reactions. None of these 24 was reexposed to the drug to which he supposedly was sensitive.

There were 9 possible instances of drug reactions during the observation period of 3 years. The most serious was a case of anaphylactic shock following an intramuscular injection with benzathine penicillin. This occurred at the initial clinic visit of a 53-year-old man who stated that he had been taking oral penicillin G daily without any untoward event during the 2 preceding months. A specimen of blood fortuitously obtained about 30 minutes prior to the "shocking" injection subsequently was found not to contain penicillin despite the patient's story that he had taken a tablet about 2 hours

before coming to clinic. For obvious reasons, this patient was placed on sulfamethoxypyridazine.

Transient hives were reported by 4 patients; 3 while on repository penicillin (1,068 injections) and one on sulfamethoxypyridazine (72 patient months). Minor skin rashes were reported by one of the intramuscular and 2 of the oral (1,104 patient months) subjects. Altogether 4 patients were transferred from either form of penicillin to sulfamethoxypyridazine.

The reasons for failure to attend clinic sessions during the first year were investigated intensively*. Intercurrent illness with or without hospitalization accounted for 39 misses. Forgetfulness, a major problem, was responsible for 19 absences while illness in the immediate family and travel accounted for 13 and 14 respectively. Other reasons were lack of transportation, lateness, difficulty in obtaining a baby-sitter and temporary incarceration by the police.

The occurrence of sore throats was compared with symptoms of other upper respiratory illnesses. The frequencies of both sore throats and upper respiratory infections were within 1% of one another for the 2 penicillin groups. Since the rates also were similar in males and females, the 2 sexes and both treatment groups will be analyzed together. (Mean values are used since for coding purposes the number of sore throats and other upper respiratory illnesses were grouped; that is, 1 to 3, 4 to 6, and so forth, per patient.)

The mean number of sore throats was 381 and of other upper respiratory episodes, 674. Since there were 2,217 clinic visits by the 2 penicillin treatment groups, there were 0.17 sore throats per patient visit as compared with 0.3 upper respiratory symptoms, in excess of 41% of the latter. The mean occurrence of upper respiratory complaints in all family members was 649, or 0.29 per patient visit, equivalent to the value calculated for the patients themselves.

Epistaxis was a relatively infrequent complaint during the 3-year period. A single severe episode occurred in a 17-year-old pregnant girl during the first trimester. Thirty-four patients (24%) sustained one to 3 episodes of minor epistaxis and 10 (7%) had more than 3 episodes. Altogether there were approximately 150 instances of minor epistaxis reported during 2,290 patient clinic visits.

Joint complaints were offered at some time by 59 (42%) of the 139 patients; slightly more occurred (probably reflecting the greater number of females) among those receiving intramuscular prophylaxis. Sixteen (28%) of 57 male patients had joint symptoms while 43 (51%) of 85 female patients had similar complaints. The knee was most commonly involved with 50 patients (36%) having complaints referable to this joint at some time during the 3-year period. The ankle, elbow, hand, shoulder and hip were complained of by 29, 27, 23, 18 and 14 patients respectively, while 7 patients had symptoms referable to the wrist and 6 to the back. Many patients had discomfort in more than one joint.

The cardiac status of 48 patients which had been ascertained at the initial visit by one of 3 physicians, was re-evaluated by the same examiner at the conclusion of the study period. The second examination was performed without knowledge of the results of the primary auscultatory findings (Table 9).

Two examiners (H.H. and T.M.) had examined the majority and found no change in two-thirds of the patients. No

*Based upon data collected by Dr. Thomas Altavilla during his tenure of a summer junior public health internship, New York State Department of Health.

changes in heart murmur were detected in 30 patients (63%) on re-examination by the same physician. Nine patients (19%) exhibited fewer or no murmurs, while 6 (12%) had one or more additional murmurs. Three patients (6%) had a different kind of murmur, but no change in number.

TABLE 9.—RESULTS OF RE-EXAMINATION OF 48 PATIENTS BY SAME PHYSICIAN AFTER INTERVAL OF ONE OF MORE YEARS

	Murmur Status				
Examiner	*No Change*	*Fewer*	*More*	*Change in Type*	*Totals*
J	3	2	1	2	8
H	12	2	3	1	18
M	15	5	2	0	22
Totals	30	9	6	3	48

The findings in these patients are particularly interesting in respect to age. Fifteen (79%) who were less than 20 years of age had no murmur changes. Two (11%) of this group had an increased number of murmurs. On the other hand, 4 or one-fifth of the patients between 20 and 39 years had an increase in the number of murmurs. Relatively few patients over 40 years of age were re-examined but 4 (45%) had fewer murmurs and none had an increased number.

The abnormal cardiac sounds detected among the clinic population have been analyzed separately. Of the 139 patients, 40 (29%) were free of murmurs on admission to the clinic and remained so throughout the study. The consensus of the several observers was that the murmurs of 69 patients (50%) remained unchanged, 7 (5%) had more and 13 (9%) fewer at the end of the study period. The auscultatory findings in 10 (7%) were unstable throughout, according to different examiners. Among 36 patients less than 20 years of age, 24 (67%) had no murmurs; only 13 (23%) of those between 20 and 39 years of age had no adventitious sounds.

Sixty-eight per cent (95 patients) of the total clinic population had at least one cardiac murmur. Thirty-seven members of this group had a single murmur; both systolic and diastolic murmurs were heard in the mitral areas of 31 persons but only 3 had 2 murmurs in the aortic area. Five patients were found to have systolic and diastolic murmurs in both the mitral and aortic areas and 10 patients were thought to have 3 different murmurs over the precordial area.

The results of the electrocardiographic and roentgenological studies are surprisingly similar for the 3 arbitrarily selected age groups. An abnormal electrocardiographic pattern was found in only 1 (4%) of 26 patients less than 20 years of age. Only one person in this same age group (not the same one) had an abnormal heart size by roentgenogram.

Fourteen patients (35%) between 20 and 39 years had abnormal electrocardiogram or roentgenological findings; many in this group had changes in both. Twenty-six patients (81%) over 40 years had abnormalities of the electrocardiographic pattern and 21 (66%) an abnormal heart size or contour.

There has been relatively little change in the functional cardiac status of most patients in the clinic. Thirteen of the 139 were lost to follow-up and one died during the study period. Of the remaining 125 persons, only 4 (3%) have had sufficient functional change to necessitate a change in their classification*. One, a 56-year-old man, ex-

*During the year immediately following the report period, 3 additional patients, all over age 40, had episodes of congestive failure and have moved from one functional category to another. For one, this was an initial episode whereas the other 2 had been in failure on other occasions.

hibited an increasing amount of cardiac insufficiency that confined him to bed and changed his functional status from Class III to IV. A 47-year-old man had an aortic lesion treated surgically and is now functionally Class II rather than I. Another man, 39 years of age, slowly has moved from Class II to III. A 53-year-old white woman with increasing cardiac decompensation has changed from Class II to III.

When 110 of the patients were specifically asked whether they noted a change in the degree of their disability while attending the clinic, 7 (6%) thought that they were more disabled, 18 (17%) that they were less disabled and 85 (77%) were unaware of any change (Table 10).

TABLE 10.—PATIENT'S CONCEPT OF CHANGE IN HIS DISABILITY STATUS SINCE ENTERING CLINIC

	Age Group							
	<20		*20–39*		*40+*		*Totals*	
Disability	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Greater	0	0	3	6	4	13	7	6
Less	5	15	6	13	7	23	18	17
Unchanged	28	38	38	81	19	64	85	77
Totals	33	100	47	100	30	100	110	100

No instance of clinical acute recurrent rheumatic fever, surprisingly, was encountered during the observation period.

Discussion. A study (Feldman[5]) of the occurrence of various Group A streptococcal types in Syracuse, New York, has been in progress for 9 years and provides information that may be pertinent to a discussion of rheumatic fever prophylaxis and epidemiology. Between 1950 and 1958, 26 Group A streptococcal types were identified but only one (T-12) was detected every year. Five types were encountered in only one and 6 in either 2 or 3 of the 9 years. Surprisingly, 7 types each accounted for 4.2% or more of the total isolations.

These data suggest that the turnover of streptococcal types is quite slow in this community (probably equally representative of others) and, therefore, the rheumatic has a limited opportunity to acquire natural immunity to a large number of types, even in a decade. He possibly "uses up" the available types in several years, which would be consistent with the classical observation that the greatest number of recurrences of acute rheumatic fever tends to occur in the first 3 years after an acute attack. This limited opportunity to develop natural immunity to a large number of types would appear to us to offer support to the policy of maintaining the rheumatic on continuing prophylaxis.

It is interesting that almost one-half of the more dependable of our patients had no throat symptoms that could be correlated with increases in their AS-O titers. This experience may be comparable with that reported by Rammelkamp *et al.*[16] who found about 40% of streptococcal throat infections to be so mild or asymptomatic as not to attract attention. On the other hand, the prophylactic regimen may have masked the clinical but not the serological expression of the infection. This also may be the reason for the less frequent occurrence of pharyngeal

complaints rather than upper respiratory symptoms among those receiving prophylactic medication, suggesting, perhaps, that bacterial pharyngitis was unusual in this population during the observation period.

The frequent AS-O increases in the absence of positive throat cultures or recurrent acute rheumatic fever may indicate that the small amount of penicillin in the circulation at any one time may be suppressing rather than preventing or eradicating streptococcal infections. Thus, the modest AS-O increase that was detected may indicate that more antigen is required to attain both high titers and clinical rheumatic fever (although the latter is not necessarily due to the same antigen).

While our data on the relation between regularity of attendance and prevention of clinical or subclinical streptococcal disease are not positive, no instance of a clinical recurrence of acute rheumatic fever was observed. Only one patient was found to have a positive throat culture and that was a month after a missed appointment. Although there has been evidence of subclinical "serological" infections, with a seasonal distribution paralleling the seasonal occurrence of streptococcal infections, the median AS-O level for the entire clinic group has been decreasing steadily.

The decline of the median AS-O values for the entire clinic population, despite the induction of new patients throughout the 3-year period, indicates that the prophylactic measures not only prevent clinical disease but reduce (or minimize) the number of subclinical infections as well. While Syracuse, New York, is in an area in which streptococcal infections are relatively common, no control population was utilized for comparison. Miller, Stancer and Massell[13] in a study of rheumatic children on prophylaxis and their unprotected siblings, found streptococcal infections to be markedly reduced among the former.

Preliminary information from a respiratory disease family study that we are conducting currently lends some support to this. By coincidence 3 of the rheumatic fever prophylaxis clinic patients are also in the family population study. These 3 female patients, aged 23, 31 and 35 years, respectively, have been completely free of streptococcal infection or evidence of subclinical infection during the first 6 months (November, 1958, through May, 1959) of the population study. During the same period, 4 of 6 members in the first family (with children ranging from 6 months to 6 years in age) had 8 positive cultures for Group A streptococci. The other 2 five-member families with children ranging from 4 to 13 years had 2 and 5 positive cultures. Thus, these 3 mothers, undoubtedly in close contact with their small children, have been protected by their prophylactic treatment apparently despite heavy exposure to streptococci.

Feinstein, Wood and Epstein[4] reported that injected benzathine penicillin was a more effective prophylactic than oral penicillin. They note, parenthetically, that each monthly injection of benzathine penicillin is sufficiently large to eradicate Group A streptococci but the same cannot be said for the relatively small oral dose. In addition, they found that streptococcal infections occurred more frequently in those patients who did not take their oral penicillin regularly. Because of the complete absence of bacteriologically proven streptococcal infections, we cannot analyze our data on this basis. When we divided our patients into "good" and "poor" attenders, we were unable to detect any differences in the incidence of serologically responsive subclinical infec-

tions. The AS-O method employed, however, is unusually sensitive.

Wright *et al.*[23] recently reported that the intramuscular injection of 1,200,000 units of benzathine penicillin G resulted in an average penicillinemia of 25 days and an average penicillinuria in excess of 100 days. In view of the exquisite sensitivity of Group A streptococci to penicillin, their data lend additional support for the superiority of repository penicillin as a streptococcal prophylactic.

The incidence of allergic manifestations to benzathine penicillin G, regardless of the route of administration, has been infrequent and not excessive both in our patients and those of most others. This is somewhat in contrast with the rather unique findings of Hsu and Evans[7] who reported that 18.6% of their 32 patients developed allergic reactions to intramuscular benzathine penicillin G. One point of difference is that almost all patients admitted to this and other rheumatic fever prophylaxis programs have had some previous exposure to penicillin. Those with histories of penicillin sensitivity were eliminated and provided with substitute programs.

Conclusions. During a 3-year period, 139 patients with either rheumatic heart disease or an acceptable history of previous rheumatic fever were provided with streptococcal prophylaxis either with benzathine penicillin G 200,000 u. daily by mouth or 900,000 u. intramuscularly at approximately monthly intervals. Each regimen appeared to be effective in preventing clinical Group A streptococcal infections and recurrent acute rheumatic fever. Modest increases in AS-O titer were noted with equal frequency in the two treatment groups and were unrelated to clinical illness. These were noted particularly in the spring months.

There was a constant downward progression of the median AS-O values for the entire population during the observation period, except that some minor increases were observed during the fall-winter season. Few allergic reactions were noted and these were of little consequence except for one episode of anaphylaxis following an initial injection. Postinjection pain and discomfort were common but not a deterrent to repeated injections. Patients who ultimately withdrew from the clinic frequently went through a period of dissatisfaction with whatever treatment was being provided for them.

ACKNOWLEDGMENT: The authors are indebted to Drs. L. Jivoff and W. Rothney and Mrs. C. Trody, R.N., Miss J. Dauphinet, R.N., Mrs. A. Hawker, Mrs. K. Collins, Misses L. Foley and P. Sheffield and Mr. B. Pakull for their invaluable clinical and laboratory aid at various times during this study. The excellent cooperation of the staff of the Syracuse Dispensary is gratefully acknowledged.

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SUMMARIO IN INTERLINGUA

Le Prevention de Recurrente Febre Rheumatic in Patientes Pediatric e Adulte per Medio de Penicillina Oral e Repositori

In le curso de un periodo de 3 annos, 139 patientes con rheumatic morbo cardiac o un acceptabile historia de febre rheumatic in le passato esseva providite de prophylaxe anti-streptococcal per le administration de penicillina G benzathina per via oral in doses diurne de 200.000 unitates o per via intramuscular in doses de 900.000 unitates a intervallos de circa un mense. Ambe programmas pareva esser efficace in le prevention de infectiones clinic per streptococcos de Gruppo A e de recurrentias de acute febre rheumatic. Esseva notate moderate augmentos del titros de antistreptolysina-O con equal frequentias in ambe gruppos de tractamento. Iste augmentos non esseva relationate a maladia clinic. Illos esseva notate specialmente durante le menses del primavera.

Un constante tendentia diminutori se manifestava in le valores de antistreptolysina-O durante le periodo de observation in le population integre, con le exception que certe minor augmentos esseva observate durante le saison de autumno e hiberno. Pauc reactiones allergic esseva notate. Istos non esseva importante, con le exception de un episodio de anaphylaxe que occurreva post un injection initial. Dolor e disconforto post-injectional esseva commun sed non satis serie pro prevenir le repetition del injectiones. Patientes obligate a quitar le clinica passava frequentemente per un periodo de dissatisfaction con le tractamento particular que esseva providite pro illes in altere locos.

IODIDE-INDUCED MYXEDEMA
REPORT OF A CASE AND REVIEW OF THE LITERATURE

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Myxedema as the result of iodide administration to a euthyroid individual is a relatively rare occurrence despite the widespread use of iodides and iodide-containing drugs. A review of the literature revealed only 22 reported cases which we felt could be considered as representing such a phenomenon. This entity is one not familiar to most physicians. Of greater importance is that the study and recognition of this process may help to shed more light on iodide metabolism and its effect on thyroid physiology.

The following case report concerns a patient in whom the relationship between iodide administration and the development of myxedema was clearly demonstrated and confirmed by reproducing the entire clinical and laboratory picture with iodides.

Case Report. J.D., a 65-year-old white male farmer, had first come to the V.A. domiciliary in March, 1957, because of an inability to support himself due to progressively increasing shortness of breath. He gave a history at that time of chronic cough productive of 2 to 6 ounces of occasionally purulent sputum and non-seasonal, intermittent wheezing of 30 years' duration.

The diagnoses of pulmonary emphysema, chronic bronchitis, pulmonary fibrosis, bronchial asthma, and late latent syphilis were made. His therapy included bronchodilators, intermittent courses of antibiotics, and iodides. Symptoms attributable to the development of myxedema were first noted on September 23, 1957, when he reported to the clinic with the complaint of hoarseness. The patient was referred to an otolaryngologist, and a diagnosis of chronic pharyngitis was made. He was first seen in medical consultation on October 10, 1957. At that time, history of marked cold intolerance, hoarseness, lethargy, dryness of the skin, and periorbital edema of 2 weeks' duration was obtained. It was estimated at that time that he had been taking 30 drops of a saturated solution of potassium iodide (SSKI) daily for 6 months. A provisional diagnosis of myxedema due to iodide ingestion was made, and the patient was referred to the hospital for studies. Iodides were discontinued on admission, and the resident physician's attention was first directed towards managing his pulmonary disease. The symptoms and physical findings of myxedema proved quite transient, and one week after stopping iodides no findings compatible with myxedema could be demonstrated. The only laboratory finding of note was a serum cholesterol of 279 mg. per 100 ml. taken 18 days following discontinuance of iodides. The basal metabolic rate (BMR) was unsatisfactory due to the patient's pulmonary insufficiency.

Since this was felt to be a rather unusual phenomenon and since iodides had always proven to be a very effective form of therapy in this patient, it was decided to reinstitute iodide therapy after appropriate base-line studies had been obtained. In January, 1958, serum cholesterol was 144 mg. per 100 ml.; fasting blood sugar, 77 mg. per 100 ml. and 24-hour thyroidal I-131 uptake, 18.7% (normal 15 to 40%). On February 1, 1958, the patient was restarted on SSKI, 15 drops t.i.d. He was closely followed in our Domiciliary Clinic, where he received ephedrine in addition to the iodides and on two occasions antibiotics to treat bacterial infections of the tracheobronchial tree. The patient took SSKI as ordered and had no symptoms suggestive

of myxedema until July 17, 1958, when he reported to the clinic complaining of minimal periorbital edema, hoarseness, and general malaise of 7 days' duration. When seen 2 weeks later, the patient had severe cold intolerance, recalled that he had noted a gradual increase in this symptom for about 3 weeks, and had worn a sweater although it was mid-summer. He had also noted marked drowsiness, lethargy, and weakness for 2 weeks. Edema of his eyelids and face, and hoarseness had progressed rapidly. There had been no change in his appetite or bowel habits.

Fig. 1.—*A*, At time of admission, July 31, 1958. *B*, Three weeks following discontinuance of iodides.

Physical examination disclosed a 65-year-old, fairly well preserved, white man who had a definite porcine appearance (Fig. 1). His face was pallid and swollen, and periorbital edema was prominent. He was obviously confused and moderately disoriented. His weight of 174 pounds was 10 pounds over his customary weight. Temperature was 98° F., pulse was 110, and blood pressure, 142/90. The patient had an extremely low-pitched, hoarse voice. The scalp hair was sparse but not coarse. There was absence of hair on the lateral aspect of his eyebrows. The skin of the forearm and hand was dry and coarse, but the integument was normal elsewhere. The thyroid gland was not palpable. Examination of the lungs showed an increase in anterior-posterior thoracic diameter and diffuse expiratory wheezes with occasional, scattered coarse rales in both bases. There were no cardiac abnormalities except for moderate sinus tachycardia. A trace of pretibial edema was noted. Neurological examination showed patellar and Achilles tendon reflexes of the delayed relaxation type.

The patient was admitted to the hospital on July 31, 1958, and the following pertinent laboratory data were obtained upon admission: Leukocyte count, 9,200 per c.mm.; differential, normal; hemoglobin, 14.6 gm.%;

total protein, 7.6 gm.% (albumin, 5.1 gm.; globulin, 2.5 gm.); blood urea nitrogen, 19 mg. per 100 ml.; urinalysis, negative for albumin and sugar; specific gravity, 1.013; microscopic examination, normal; serum cholesterol, 375 mg. per 100 ml. (51% esters); V.D.R.L., 4 plus. Electrocardiogram on August 4, 1958, was abnormal, showing generalized nonspecific T wave abnormalities (Fig. 2). Chest roentgenogram revealed pulmonary emphysema and fibrosis but no cardiomegaly.

The patient was maintained on SSKI, 15 drops t.i.d., while all the routine and special studies, which are described separately, were obtained. The BMR was again unsatisfactory because of dyspnea. Meanwhile, the clinical

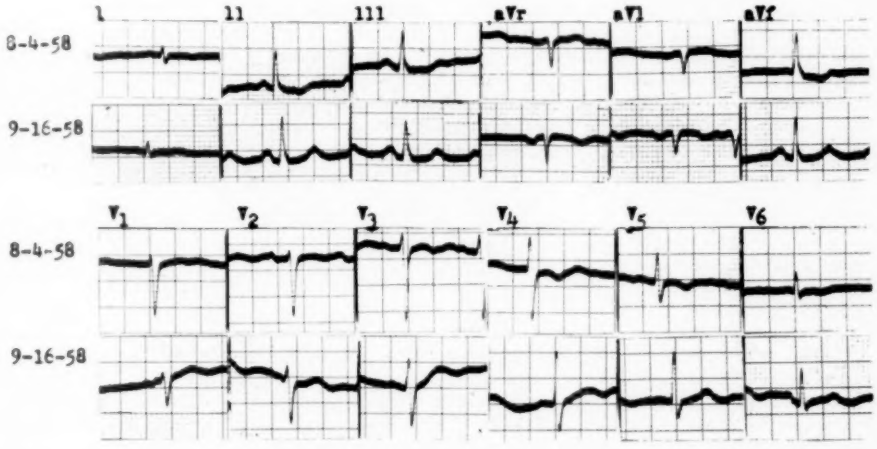


Fig. 2.—8/4/58. ECG at time of admission with clinical myxedema. Note the generalized T wave inversion of limb and precordial leads. 9/16/18—25 days following discontinuance of iodides. Note the return of ECG pattern to normal.

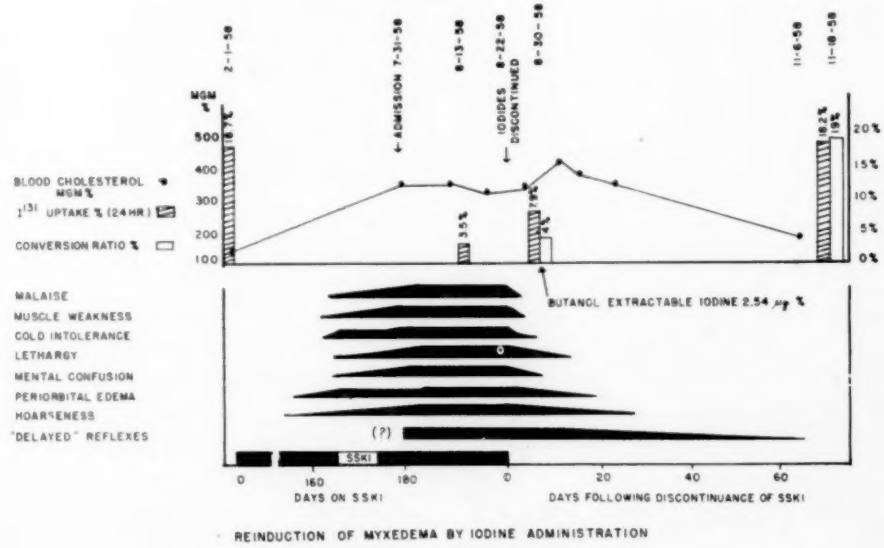


Fig. 3

signs of myxedema progressed. Iodides were discontinued on August 22, 1958. The relationship of symptoms, clinical findings, and laboratory data to iodide administration and discontinuance is shown in Fig. 3.

On the 4th day after the discontinuation of iodides the patient subjectively felt much better, although no objective changes were observed. The serum cholesterol, however, continued to rise for 10 days and then began to fall. It was apparent that the second spontaneous recovery from myxedema was prolonged compared to the previous episode, and it was over a week before his mental confusion disappeared. The periorbital edema improved markedly after 10 days, but did not disappear completely until 3 weeks had elapsed (Fig. 1). The hoarseness persisted for at least 4 weeks. Cold intolerance diminished rapidly and disappeared within 10 days. Electrocardiogram taken on September 16, 1958, 4 weeks following discontinuance of iodides, showed marked improvement of T waves in all leads (Fig. 2).

On the first clinic visit after discharge (September 17, 1958), one of the authors felt that he could detect the tip of the thyroid gland deep in the substernal notch, but this was not palpated on subsequent examinations. The delayed relaxation type of Achilles tendon reflex became increasingly difficult to elicit after 3 weeks but persisted for 6 weeks.

He was seen again in November, 1958. The patient's only complaints at that time were referable to his chronic lung disease. His serum cholesterol had dropped to 191 mg. per 100 ml. (67% esters). The 24-hour thyroidal I-131 uptake was 18.7%, with a conversion ratio of 19% (normal 10 to 40%). The protein bound iodine was 6.6 μg.% (normal 3.5-7.5 μg.%). The patient was continuously observed at the Domiciliary Clinic and remained free of symptoms of myxedema.

The patient was readmitted to the hospital on January 1, 1959, with a recurrence of his chronic pulmonary infection, the development of pretibial pitting edema, and a marked increase in dyspnea which was felt to be secondary to cor pulmonale. There were no symptoms or physical findings to indicate thyroid dysfunction. The patient was treated with antibiotics, digitalis, and diuretics. He improved for the first 3 days, but on the 4th day the patient developed peripheral vascular shock and expired.

Necropsy revealed subacute tracheobronchitis with bronchiectasis, pulmonary emphysema, and pulmonary edema. There was evidence of moderate coronary atheromatosis and cardiomegaly (520 gm.) involving both right and left ventricular chambers. No pericardial effusion was demonstrated. Microscopic sections of the thyroid were described in the following fashion by our pathology consultant:*

"Multiple sections from this thyroid gland all showed an essentially similar picture. This picture is a rather complex one, consisting of areas of rather hyperactive-looking acini scattered among essentially normal acini. Some of these areas are associated with patchy and irregular fibrosis and areas of lymphocytic infiltration. These changes, although somewhat unusual, are to be expected in a small proportion of people of the age of this patient.

"One other change, however, is not consistent with this, and that is the presence of small groups of irregularly shaped small acini which are either devoid of colloid, or else contain a small amount of thin, poorly stained colloid. These areas would be consistent with the suggested diagnosis of iodide-induced hypothyroidism."

The gland was grossly normal, weighing 16 gm. Sections of the pituitary gland were regarded as normal.

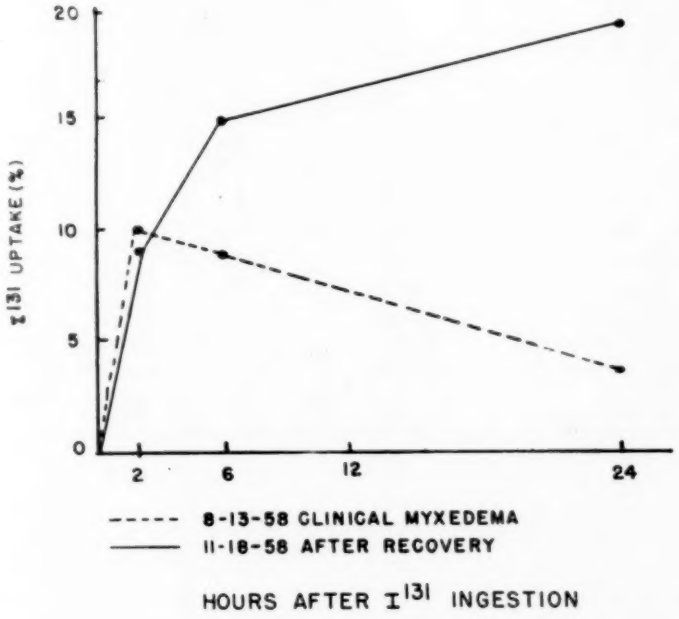
Special Laboratory Findings in the Present Case and as Reported in the Literature. THYROIDAL RADIOIODINE UPTAKE. Little significance can be attached to a depressed 24-hour thyroidal radioiodine uptake value itself in patients on iodine therapy. As expected, this test revealed an abnormally low uptake in our patient while he was on iodides: a finding noted in 7 of the 11 other cases in which this study was reported (Table 1).

However, when the uptake of radioiodine was measured at earlier intervals, it proved quite revealing (Fig. 4), and evidence for an active iodide-trapping mechanism and equally active iodide turnover was found. Although the 2-hour I-131 uptake was only 10% in our patient, this figure must have represented a very high quantity of total iodide trapping because of the

*Colin R. MacPherson, M.D., Assistant Professor of Pathology, Ohio State University.

huge store which was present at that time. For example, the trapping of 100 μg. of iodine in 2 hours from a readily available pool of 1000 μg. would represent an uptake of 10%, but the ingestion of 1500 *mg.* of iodides daily would cause such a marked increase in available iodides that a 10% uptake would indeed represent a high figure. The cumulative type of curve that was obtained in our patient after a euthyroid status had been restored. A comparison of the two curves in our patient is demonstrated in Fig. 4.

THYROIDAL RADIOIODINE UPTAKE: REBOUND PHASE. A rise in 24-hour radioiodine uptake to abnormal levels from 1 to 12 days following discontinuance



COMPARISON OF I^{131} ACCUMULATION PATTERN DURING AND AFTER RECOVERY FROM IODIDE-INDUCED MYXEDEMA

Fig. 4

decreasing counts at 6 and 24 hours are thus also evidence for a large turnover of iodides by the thyroid gland. Similar and often more striking thyroidal radioiodine uptake curves were described by others who studied patients still on iodides or immediately after discontinuance of iodides (Cases 5, 16, 18, 19, 20, 21 and 22). This type of thyroidal uptake curve contrasts sharply with the expected normal of iodides has been frequently reported in cases where these studies were done (6, 7, 8, 18, 19, 20, 21, 22). In our patient the 24-hour radioiodine uptake rose only from 3.5% to 7.8% seven days after discontinuing iodides, and we failed to demonstrate this response. The I-131 conversion ratio was also depressed at this time and further was suggestive of a failure of the gland in our patient to recover as rapidly

from the blocking effects of iodides as in most of the reported patients.

RESPONSE TO THYROIDAL STIMULATING HORMONE (TSH). The administration of 60 units of TSH over a 5-day period, while iodide therapy was continued, failed to increase the 24-hour radioiodine uptake. Unfortunately, 2- and 6-hour uptakes were not obtained and we feel that any conclusions from the 24-hour uptake alone would be invalid as discussed previously.

BUTANOL-EXTRACTABLE IODINE. The butanol-extractable iodine test would be one of the few tests of merit in determining thyroidal function in the presence of iodide therapy but was used infrequently. The value for this test in our patient was 2.5 μg.% (normal 3.2 to 6.4 μg.%) one week after discontinuing iodides. In the 2 other cases (16 and 19) in which this study was reported the results also correlated well with the clinical picture of myxedema.

Review of Literature. Twenty-two instances of iodide-induced hypothyroidism have been reported previously (Table 1). Hurxthal[8] was the first to call attention to this phenomenon in 1945. He described the development of hypothyroidism in a 6-year-old girl who received Lugol's solution for 2 months as therapy for a simple goiter (Case 1). Remission from the hypothyroid state occurred when the administration of iodine was discontinued. In 1952, Bell[1] collected 4 cases of goiter formation following iodide administration and noted that 3 of his cases became hypothyroid. Regression of thyromegaly and restoration of euthyroidism were effected in all of his patients by therapy with desiccated thyroid. Two patients (Cases 3 and 4) remained euthyroid after discontinuance of thyroid extract. Surgical removal of the goiter in his first case (Case 2) showed it to be of the colloid type. Raben[14] discussed the development of goiter and myxedema in a 42-year-old woman 9 months after she had received an organic iodine compound (Lipiodol) during bronchography (Case 5). In this patient the high serum iodide level was shown to be due to the slow absorption of iodine from Lipiodol persisting in the lung. Morgans and Trotter[10] reported on 2 extremely well-documented cases. In both patients (Cases 6 and 7) manifestations of myxedema disappeared very rapidly after iodide withdrawal alone. In one patient (Case 6), goiter formation was not detected. This patient was later re-treated with iodides during the ensuing 9 months but myxedema did not recur. Goldner, Adesman and others[6] commented upon a similar case (Case 8) in 1955 and remarked that hypothyroidism "was reinduced in a few weeks" by the readministration of iodine. Turner and Howard[19] reported the development of goiter in 13 children and adolescents receiving iodides. Of these, 7 had hypothyroidism (Cases 9 to 15) and had been taking 10 to 1500 mg. of iodides daily for periods of from 2 to 5 years as therapy for bronchial asthma. All became euthyroid and had a reduction of their thyromegaly following treatment with thyroid extract. Microscopic examination of the thyroid gland in one of their patients (Case 10) showed "hyperplasia and lack of colloid formation." Later Hydovitz and Rose[9] (Case 16) cited a patient with severe myxedema who responded only partially to iodide withdrawal and eventually required maintenance thyroid hormone. They were able to demonstrate a basic defect in thyroxin formation in their patient long after discontinuing iodides. A patient in whom iodide-induced myxedema developed in the absence of enlargement of the thyroid was reported by Skaggs and Cooke[17] in 1956

(Case 17). In 1957 a carefully studied instance of goiter formation, myxedema, and recovery from both after iodine withdrawal was described by Rubinstein and Oliner[16] (Case 18).

In 1958 Paley, Sobel and Yalow[12] made an intensive study of a patient with iodide-induced hypothyroidism and goiter. They demonstrated, with needle biopsy, hyperplasia of the gland despite clinical findings of hypothyroidism, and by laboratory studies revealed increased iodide trapping but blockage of organic binding (Case 19).

Most recently, Paris *et al.*[13] reported on 5 patients who, following prolonged treatment with iodides for asthma, developed diffuse goiters. Hypothyroidism developed in 3 of these patients (Cases 20 to 22). Needle biopsy of the glands revealed parenchymatous hypertrophy in all cases. Radioiodine studies done 20 hours after iodide withdrawal in one patient showed that I-131 cleared by the thyroid gland was in equilibrium with blood I-131. This finding was interpreted as evidence that organic binding of iodide had been blocked and was confirmed 24 hours later by radioautographic studies on a biopsy of the thyroid.

A summary of the 22 described cases permits certain generalizations regarding the syndrome and also allows comparison of various characteristics of this condition with those observed in our case.

FREQUENCY. The paucity of reported cases contrasts with the known widespread usage of iodine-containing compounds and in itself suggests that euthyroid individuals developing hypothyroidism as a result of iodine administration may have an underlying defect in thyroid metabolism which is brought out by iodine ingestion. On the other hand, the fact that certain authors have been able to accumulate groups of patients displaying the syndrome is suggestive that it may occur more commonly than generally appreciated but often escapes diagnosis. Additional cases were not discovered among our population of iodine-treated patients in spite of an active search of over a year's duration.

AGE AND SEX FACTORS. Although half of the reported instances of iodide-induced myxedema occurred in subjects under the age of 20 years, all decades of life from the first to the seventh were represented. Similarly, no sex differentiation was noted as each sex was represented equally.

DATA REGARDING IODIDE ADMINISTRATION. Iodine in many chemical forms was utilized in the reported cases. Lugol's solution, SSKI, syrup of hydriodic acid, and organic iodides including iodopyrine and Lipiodol were specifically mentioned. Iodides were most often prescribed as treatment for bronchial asthma. Estimation of the daily dose was possible in two-thirds of the previously reported cases. Intake ranged from 5 to over 2500 mg. of iodides daily. The rapidity of induction of the syndrome bore no relationship to the daily dose.

A more definite relationship was found with regard to the duration of iodide intake and development of the syndrome. With the exception of one case with a 2-month interval, all the rest exceeded 6 months before onset of myxedema, and in two-thirds of the cases the duration of iodide therapy ranged from one to 5 years.

The physician is never entirely certain that any patient faithfully takes a medication daily, and the factor of whether or not intake was continuous must be considered in evaluation of time factors. Hypothyroidism was reinduced in our patient only after 160 days of continuous administration of approximately 1500 mg. of iodides daily, and clinical recovery from myx-

TABLE I

SUMMARY OF REPORTED CASES OF IODIDE-INDUCED MYXEDEMA

CASE	AUTHORS	YEAR	AGE	SEX	DATA REGARDING ADMINISTRATION OF IODIDES			CLINICAL STATUS BEFORE THERAPY		CLINICAL STATUS DURING IODIDE ADMINISTRATION				THERAPY AFTER DIAGNOSIS OF MYXEDEMA ESTABLISHED		CLINICAL STATUS AFTER THERAPY			
					REASON	DAILY DOSE (mg.)	DURATION	GOITER	EUTHYROID	GOITER	MYXEDEMA	SERUM CHOL (mg.%)	BMR (%)	IODINE STOPPED	DESICCATED THYROID (gr.)	GOITER	EUTHYROID	SERUM CHOL (mg.%)	BMR (%)
1	HURXTHALL	1965	6	F	Goiter	-	2 mo	+	-	+	+	432	-	Yes	0	0	+	179	-
2	BELL	1952	11	F	Asthma	-	½ yr	0	+	++	+	332	-35	No	30	+	+	200	-
3	BELL	1952	23	F	Asthma	--	4 yr	0	+	++	+	181	-18	Yes	60	0	+	83	-
4	BELL	1952	31	F	Goiter	--	7 yr	+	+	++	+	253	-33	Yes	30	+	+	-	-
5	RABEN	1952	42	F	Bronchiectasis	-	9 yr	0	+	+++	+	405	-	Yes	180	0	+	219	-
6	MORGAN & TROTTER	1953	66	M	Rheumatism	180	1 yr	0	+	0	+	370	-15	Yes	0	0	+	200	-2
7	MORGAN & TROTTER	1953	45	F	Asthma	2500+	4 yr	0	+	+++	+	300	-21	Yes	0	0	+	150	-
8	GOLDNER & ADESMAN	1955	60	F	Asthma	-	30 yr	0	+	+	+	433	-	Yes	0	0	+	-	-
9	TURNER & HOWARD	1956	5	M	Asthma	150	2½ yr	0	+	+++	+	-	+6	Yes	30	±	+	-	-
10	TURNER & HOWARD	1956	8	F	Asthma	225	1½ yr	0	+	++++	+	-	-12	No	30	+	+	-	-
11	TURNER & HOWARD	1956	15	M	Asthma	225	2½ yr	0	+	++	+	-	-32	Yes	60	0	+	-	-
12	TURNER & HOWARD	1956	9	M	Asthma	240	2 yr	0	+	++	+	-	-	Yes	30	0	+	-	-
13	TURNER & HOWARD	1956	16	F	Asthma	900	4 yr	0	+	+++	+	-	-	Yes	60	+	+	-	-
14	TURNER & HOWARD	1956	17	M	Asthma	1500	5 yr	0	+	+++++	+	-	-30	Yes	60	+	+	-	-
15	TURNER & HOWARD	1956	11	M	Asthma	10	3 yr	0	+	++	+	-	-3	Yes	130	±	+	-	-
16	SYDOVITZ & ROSE	1956	52	M	Asthma	3-5	+12 yr	0	+	++	+	273	-28	Yes	+	++	+	-	-
17	SKAGGS & COOKE	1956	69	M	Asthma	600	3 yr	0	+	0	+	417	-29	Yes	30	0	+	175	-9
18	RUBINSTEIN & OLINER	1957	33	F	Asthma	244	6 yr	0	+	++	+	300	-21	Yes	0	0	+	129	+12
19	PALEY, ET AL	1958	57	F	Asthma	-	4 yr	0	+	+++	-	308	-22	Yes	+	0	+	303	+2
20	PARIS, ET AL	1959	--	M	Asthma	-	prolonged	0	+	++	+	-	-	Yes	0	0	+	-	-
21	PARIS, ET AL	1959	--	F	Asthma	-	prolonged	0	+	++	+	-	-	No	+	0	+	-	-
22	PARIS, ET AL	1959	--	-	Asthma	-	prolonged	0	+	++	+	-	-	No	+	0	+	-	-
23	TAGUCHI & SKILLMAN	1959	65	M	Asthma	1500	6 mo	0	+	0	+	400	-	Yes	0	0	+	130	-

* Post Thyroidectomy

edema occurred fairly rapidly after its withdrawal. These findings would support the thesis that iodide-induced hypothyroidism may occur only after prolonged iodide intake which must be essentially uninterrupted. Two exceptions were noted, however, when attempts to reinduce myxedema were made. In Case 8, hypothyroidism was "reinduced after a few weeks." However, details were not given. In Case 21, mild myxedema was reinduced in 5 weeks.

CLINICAL STATUS DURING IODIDE THERAPY. All of the collected cases were presumably euthyroid prior to ingestion of iodides and with the exception of Cases 2 and 4 thyromegaly was not present. During therapy, all of the previously reported patients except Cases 6 and 17 developed palpable enlargement of the thyroid gland which was pronounced in many instances. The lack of goiter formation in our patient, as in Cases 6 and 17, was therefore of special interest and indicates that this syndrome may occur without thyromegaly. The severity of iodide-induced hypothyroidism varied, but it is clear from descriptions of the reported cases and evaluation of our patient that severe myxedema clinically indistinguishable from spontaneous myxedema may be precipitated. The diagnosis of the syndrome appears to rest chiefly on clinical grounds, since many of the usual tests of thyroid function are invalidated by the high serum iodide levels. Although some authors report striking depression of the basal metabolic rate, attainment of the basal state is not always possible in subjects with bronchial asthma. Elevation of serum cholesterol concentration appears to be the most practical laboratory method for both diagnosis and estimation of response to iodide withdrawal. Nine of the 12 cases in whom serum cholesterol determinations were made showed values of 300 mg. per 100 ml. or more. In nearly all instances, where comparison of cholesterol levels during hypothyroidism and after recovery were made, significant decreases were observed. Other aids such as estimation of butanol-extractable iodine were infrequently employed.

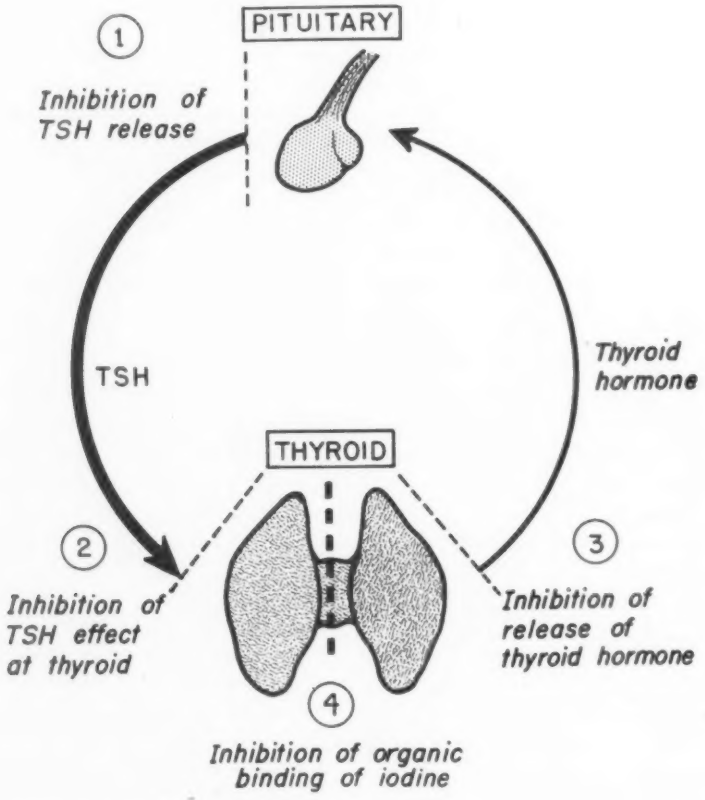
RESPONSE TO TREATMENT. We feel that the available data would indicate that iodide withdrawal alone would probably have resulted in complete recovery from myxedema in all the cases, with the exception of those who had thyroidectomies (Cases 2 and 10), and the patient described by Hydovitz and Rose[9] (Case 16). In the latter patient desiccated thyroid had to be administered to effect complete recovery, although definite improvement had occurred with iodide removal alone. To explain this they favored the possibility of an intrinsic metabolic defect of the thyroid gland complicated by iodide administration but also considered the possibility of persistent alteration secondary to the effects of iodine alone.

It would also appear that in nearly all of the reported cases with thyromegaly secondary to iodide ingestion, with or without myxedema, there would have been disappearance or at least a marked decrease in size of their goiter on iodide discontinuance alone.

The time necessary to establish a state of euthyroidism after cessation of iodine intake was noted infrequently but often was less than one month. In our patient the severe manifestations of myxedema regressed within a 3-week period.

HISTOLOGICAL DATA. Histological studies of the thyroid gland utilizing needle biopsy, thyroidectomy, and postmortem examination were available in 8 of the 22 reported cases of iodide-induced myxedema. In 2 cases (2 and 6) colloid goiters were reported. In the former case the goiter was removed

when the patient was euthyroid and in the latter case the thyroid gland was examined at postmortem examination long after recovery from myxedema. An essentially normal thyroid gland was described at postmortem examination in Case 18 but again long after euthyroid status had been restored. However, in the remaining 5 cases (10, 19, 20, 21 and 22) tissues were studied while the patient had signs of myxedema, and in all instances the thyroid gland was described as showing hyperplasia. These findings correlate well with the clinical evidence of thyromegaly and the laboratory findings of an over-active iodide-trapping and turnover mechanism suggesting an increased TSH effect. This histological appearance of the thyroid gland in our patient, approximately 3½ months after clinical recovery from myxedema, was a complex one but could be considered as showing changes consistent with recovery from a hyperplastic state.



SOME THEORETICAL MECHANISMS FOR IODIDE-INDUCED MYXEDEMA

Fig. 5

Pathophysiology. The physiologic effects of iodine on thyroid gland function have been exhaustively studied. Most of the data have been obtained from the study of animals and hyper-

thyroid man. The mechanisms by which hypothyroidism is induced in euthyroid man are imperfectly understood. For discussion purposes one might consider that iodides could induce hypothyroidism in the euthyroid subject by inhibition of the pituitary-thyroid axis in one or more of several areas (Fig. 5).

1. INHIBITION OF RELEASE OF TSH BY THE PITUITARY. This hypothesis appears to be supported by the experiments of Del Conte and Stux[4] who reported that the administration of iodides to intact rats reduced blood concentrations of TSH as measured by their assay. Since most patients with iodide-induced myxedema have goiters and laboratory evidence of an increased iodide trapping capacity, an increased rather than decreased TSH effect is suggested. These findings are, however, inconsistent with the above hypothesis.

2. INHIBITION OF TSH EFFECT AT THE THYROID LEVEL. This possibility is suggested by the work of Rawson[15] who found that the usual TSH effect of increasing thyroid acinar cell height in the hypophysectomized rat was lost when iodides were administered. Again, however, the finding of hyperplastic goiters and clinical evidence of an increased iodide trapping capacity in patients with the syndrome under discussion seem to refute this mode of action.

3. INHIBITION OF RELEASE OF THYROID HORMONE. This possibility might be supported by the work of Goldsmith and Eisele[7], who reported that the administration of iodides to hyperthyroid patients whose synthesis of thyroid hormone had been blocked, resulted in a decreased rate of thyroid hormone release. This effect remained even when TSH was administered. They suggested that this phenomenon might be explained by blocking of TSH effect at the thyroid gland. De Robertis and Nowinski[5] also suggested from their studies that the release of thyroxin from thyroglobulin was inhibited by iodide. However, Benua and Lipsett[2] found iodides exercised no effect on the rate of thyroid hormone release in hypophysectomized patients who were given fixed doses of TSH while thyroid hormone synthesis was blocked by propylthiouracil.

4. INHIBITION OF THYROID HORMONE SYNTHESIS. Rubenstein and Oliner[16] have comprehensively reviewed the several possible mechanisms and favor the hypothesis that persistently high levels of plasma iodide induce a block in thyroid hormone synthesis. They cited the works of Morton, Chaikoff and Rosenfeld[11], Wolff *et al.*[20], Stanley[18], and Childs *et al.*[3], who each showed that large concentrations of iodides tend to block organic binding of iodine. The more recent studies of Paris *et al.*[13], Paley, Sobel and Yalow[12], Rubenstein and Oliner[16] and of Morgans and Trotter[10] also support this thesis. There appear to be no clinical or experimental data which convincingly negate this hypothesis but the exact chemical mechanism by which the block in organification of iodine is induced remains somewhat obscure.

Summary. Myxedema resulting from iodide administration to a euthyroid individual is a relatively rare occurrence, despite widespread use of iodides and iodide-containing drugs.

The case of a 65-year-old man is presented in whom myxedema resulted from prolonged iodide ingestion for chronic lung disease. Prompt recovery followed discontinuance of iodides and this relationship was clearly demonstrated when the entire clinical and laboratory picture of myxedema was reproduced by readministration of iodides.

A review of the literature revealed 22 reported cases of this phenomenon.

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The clinical features of myxedema varied from mild to severe and were indistinguishable from spontaneous myxedema except for the very high incidence of goiter formation. The dosage of iodine was as low as from 3 to 5 mg. daily, and the forms in which administered unimportant, but a constant ingestion over a fairly prolonged period appeared to be essential. Discontinuance of iodides alone would appear to be sufficient in most cases to produce a fairly prompt remission to a euthyroid status and cause regression of the goiter.

Radioiodine studies proved to be of special interest. Although 24-hour radioiodine uptake studies were usually low, uptake studies at earlier increments were indicative that these glands were actually hyperactive as far as iodide trapping and turnover. Repeat radioiodine studies done one to 12 days following discontinuance of iodides usually demonstrated a striking rebound with 24-hour uptake rising to abnormally high levels.

The available histological findings were suggestive that parenchymal hyperplasia of the thyroid gland secondary to increased TSH effect was the explanation for the above radioiodine results as well as for the presence of thyromegaly in iodide-induced myxedema.

The exact pathologic physiology of this type of myxedema remains obscure. However, it would appear most probable that high levels of iodide inhibit thyroid hormone synthesis by interfering with organic binding. The rare occurrence of this phenomenon would also suggest that this occurs in individuals whose thyroid glands are unusually susceptible to the inhibitory effects of iodide.

ACKNOWLEDGMENTS: The authors wish to thank Dr. George J. Hamwi, Professor, College of Medicine, and Chief, Division of Endocrinology and Metabolism, Ohio State University; and Dr. Robert M. Blizzard, Assistant Professor, Pediatrics, The Children's Hospital, Columbus, Ohio, for helpful criticism and advice; Miss Pauline Franks and her staff of the Research Service for patience and diligence in typing the manuscript; and Mr. F. J. Van Dyke of Medical Illustration Service for preparing the illustrations.

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SUMMARIO IN INTERLINGUA

Myxedema Inducite per Iodo
Reporto de un Caso e Revista del Litteratura

Myxedema resultante del administration de ioduro a un subjecto euthyroide es relativemente rar, in despecto del extense uso de ioduros e drogas continente ioduros.

Es presentate le caso de un masculo de 65 annos de etate in qui myxedema resultava ab le prolongate ingestion de ioduro como tractamente de chronic morbo pulmonar. Prompte restablimento del patiente sequeva le cessation del uso de ioduros, e iste relation esseva clarmente demonstrate quando le complete tableau clinic e laboratorial de myxedema esseva reproducite per le re-administration del ioduros.

Un revista del litteratura ha revelate 22 reportate casos de iste phenomeno. Le aspectos clinic de myxedema variava inter leve e sever e non esseva distinguibile ab myxedema spontanee, excepte que il habeva un altissime incidentia de formation de struma. Le dosage diurne de iodo esseva in certe casos non plus que 3 a 5 mg. Le forma de administration esseva sin importantia, sed un constante ingestion durante un satis prolongate periodo de tempore pareva esser essential. In le majoritate del casos, le cessation del administration de ioduros suffice apparentemente pro effectuar un satis prompte remission al stato euthyroide e pro causar le regression del struma.

Studios con iodo radioactive esseva specialmente interessante. Studios del acceptation de radio-iodo in 24 horas produceva generalmente basse valores, sed studios effectuate post plus curte intervallos indicava que le glandulas thyroide esseva hyperactive quanto al captation e metabolisation del ioduros. Repetitiones del studios a radio-iodo 1 a 12 dies post le cessation del administration de ioduro demonstrava usualmente un frappante resalto, con le valores pro le acceptation de iodo in 24 horas attingente anormalmente alte nivellos.

Le disponibile constatationes histologic suggere que hyperplasia parenchymal del glandula thyroide, secundari al augmentate effecto de hormon de stimulation del glandula thyroide, esseva le explication del supra-mentionate resultatos del studios a radio-iodo e etiam del presentia de thyromegalia in myxedema causate per ioduros.

Le precise pathophysiologia de iste typo de myxedema remane obscur. Tamen, il pare plausibilissime que alte nivellos de ioduro inhibi le synthese de hormon thyroide per interferer con le ligation organic. Le raritate del phenomeno pare etiam suggerer que illo occurre in subjectos con glandulas thyroide que es inusualmente susceptibile al effectos inhibitori de ioduro.

PULMONARY AND ALLERGIC MANIFESTATIONS OF CYSTIC FIBROSIS OF THE PANCREAS*

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and

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Cystic fibrosis of the pancreas, sometimes referred to as mucoviscidosis, is a disease which usually comes only to the attention of pediatricians. However, the diagnosis is being made more often now in young adults and so it was thought interesting to present our findings in a small group of cases. The reasons given for the apparent increase in incidence are a greater awareness of the condition and more efficient therapeutic measures which allow many of the children to reach adult life.

The first complete description of the disorder was given by Dr. Dorothy Andersen in 1938[1]. She presented clinical and pathologic material on 45 patients and demonstrated a correlation between the steatorrhea, involvement of the bronchopulmonary tree and extensive cystic and fibrotic changes in the pancreas. Of the 25 children who lived longest, yet died between 6 months and 14½ years, death was due always to purulent bronchitis, bronchiectasis or bronchopneumonia, and *Staphylococcus aureus* was isolated also from most of those whose infections were cultured. Asthma has been noted frequently in this disease by several authors (Derbes, Dent and White[3], Glaser[9], Sherman and Kessler[13]) and has been generally assumed to be due to obstruction of the bronchi by the viscid secretions, and aggravated by secondary infection and edema. Certain manifestations compatible with vitamin A deficiency were noted in some patients, a finding of possible significance in the pathogenesis of the pulmonary lesions. For some years following this study the chief emphasis, from a diagnostic standpoint, was placed on the finding of lowered pancreatic enzymes in the duodenal contents. More recently, however, these children have been shown to have an elevation of the sodium and chlorides of the sweat, a finding that is sufficiently uniform to be taken as the chief diagnostic tool. In spite of its obvious importance, the mechanism by which this abnormality occurs has not been clarified. (Data pertinent to these tests and to our own report are to be found in references (Andersen[1,2], Derbes, Dent and White[3], di Sant 'Agnese *et al.*[4,5,6], Feinerman and Burke[7], Glaser[9], Gochberg and Cooke[10], Kulczycki, Craig and Shwachman[11], McIntosh[12], Sherman and Kessler[13], Shwachman and Kulczycki[14]). Various methods

*Supported in part by the National Institute of Allergy and Infectious Disease, U.S. Public Health Service (Training Grant 2E-9), and the Upjohn Company Fellowship Grant in Allergy. Read in part at the meeting of the American Clinical and Climatological Association at Hot Springs, Virginia, on November 2, 1959.

for the collection of sweat have been used, but the most practical would seem to the one recently described by Gibson and Cooke[8]. This test is done by iontophoresis of pilocarpine in a localized area of the skin, the sweat being collected on filter paper disks, then weighed and analyzed.

An additional striking feature of this disease, revealed by recent studies (Trever and Abrahams[15], Van Metre *et al.*[16]) is the presence of allergic manifestations of the atopic type. As mentioned above, asthma referred to by some authors (Derbes, Dent and White[3]) as the "intrinsic" type related to viscid secretions and infection has been emphasized in previous reports; no reference, however, to atopic asthma and allergic rhinitis, eczema, and others, was ever made. A high incidence of such atopic conditions was found in older patients in this survey who had survived and reached their teens. These atopic manifestations, especially hay fever and asthma with positive skin reactions, may divert attention from and mask the underlying disease, which may be suspected later, when pulmonary complications related to increasingly severe infections dominate the clinical picture.

Some of the significant features of this disease, including the allergic manifestations may be illustrated by brief reports of 2 young adults whose clinical courses have been of considerable interest.

Case Reports. CASE 1. D.H., a white girl, who is now 21, was first seen by one of us (W.L.W.) at the request of the Department of Otolaryngology in August, 1952. The patient was 14 years of age and presented with nasal and antral polyps, and chronic sinusitis accompanied by chronic cough but no asthma. The past history revealed the presence of foamy stools since infancy and alleged allergy to certain foods; however, symptoms of both disturbances subsided on administration of Pancreatin tablets, and improvement in general health followed. Some form of chronic rhinitis, repeated "colds" and cough confined, primarily, to the winter months developed at an early age. A tonsillectomy was done at the age of 4 and again at 8. At the age of 6 she was examined at a University hospital where allergy studies revealed positive skin reactions to various inhalants and foods. A diet was imposed and desensitization was carried on for 2 years without definite improvement. At age 10, a febrile illness, diagnosed pneumonia, was followed by lingering mild fever and cough for several months. Nasal polyps had been excised at the ages of 8 and 12. Typical symptoms of hay fever during the tree, grass and ragweed seasons started at the age of 11. Similar symptoms developed on contact with animals. Bronchitic attacks had occurred during the winter and for 3 years during the spring and fall; some of the latter were, apparently, triggered by pollen sensitivity. Antibiotics had been used frequently, and antihistamines for the allergic rhinitis. On examination the patient was found to be a little thin, the fingers were tapering but not definitely clubbed; lymph glands were not remarkable, and the spleen was not palpable. Some increased dorsal kyphosis and increased a-p diameter of the chest were obvious; the breath sounds were moderately prolonged and accompanied by a few scattered sibilant squeaks. The hemogram was normal; blood eosinophils were not increased. O.T. was mildly positive in a dilution of 1:1000. Roentgenogram of chest revealed diffuse infiltration of both lungs, more marked on the right, on which side in the lower half a shadow, the size of a 50-cent piece, was interpreted as being compatible with pneumonia. Roentgenogram of the sinuses revealed diffuse clouding of the antra with cartilaginous septa in both; no fluid level was seen. Skin tests by the intracutaneous method elicited typical immediate reactions in high dilution to the pollens, dust, feathers, kapok and wool, and to several fungal spores. The patient was admitted to the hospital where nasal polyps were excised and a bilateral radical antral operation was performed. Convalescence was satisfactory. Desensitization to pollens, inhalants and molds was instituted and continued to January, 1958. Respiratory infections continued to recur, particularly, in the spring and fall coincident with the tree and ragweed pollen seasons. In general, however, the patient made good progress for 5 years, taking antibiotics and short courses of Meticorten for the episodes of infection, and continuing Pancreatin tablets. In the fall of 1957, two attacks of pneumonitis were followed by

chronic cough and expectoration which led to her second admission to the hospital in January, 1958. At that time she was acutely ill with temperature of 102° to 103°, pulse 120 to 140 and respirations 28 to 38. The physical signs showed a severe degree of emphysema, bronchopneumonia, hepatomegaly, and clubbing of fingers and toes; the spleen tip was just palpable. Roentgenograms of the chest confirmed the physical findings and demonstrated changes in the upper lobes suggestive of cavities (Fig. 1). The most significant laboratory findings were: a heavy growth of a mucoid type of pseudomonas from the sputum, a high serum gamma-globulin, and a sweat test in which the chlorides were elevated to 80 mEq. per L. This was considered a positive test for cystic fibrosis of the pancreas. This test not only confirmed our diagnosis but that of Dr. H. Clarkson Meredith, her family physician in Norfolk, Virginia. The patient responded promptly to a regimen which included three antibiotics, digitalization and Meticorten. Improvement was noted in the chest film (Figs. 2 and 3). She was discharged after 2½ weeks' hospitalization. At home she continued her regular medicines which included alphatocopherol and Pancreatin, and maintenance doses of 10 mg. per day of prednisone. Terramycin, 2 gm. a day, was advised in case of any acute infection. She was last seen as an outpatient in March, 1959, at which time no new findings were uncovered. The same organism was isolated from the sputum and, because it was moderately sensitive to Terramycin, this antibiotic was again advised for acute respiratory infections.*

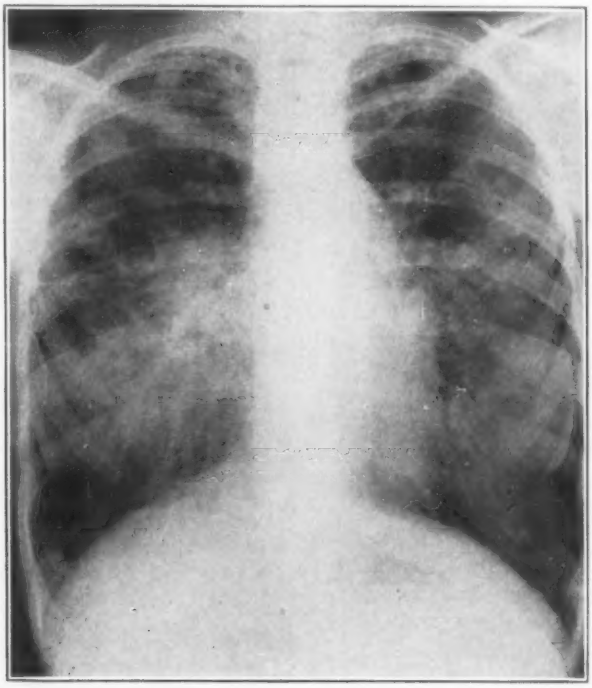

Fig. 1.—Chest film of D.H. on admission February 6, 1958, demonstrating emphysema, bronchopneumonia and cavities or bullae in upper lobes. Cardiac contour suggests right-sided hypertrophy.

*Dec. 4, 1959. Information has recently been received that the patient has been making excellent progress on vitamin A and Pancreatin, maintenance corticosteroid therapy, and periodic administration of antibiotics.

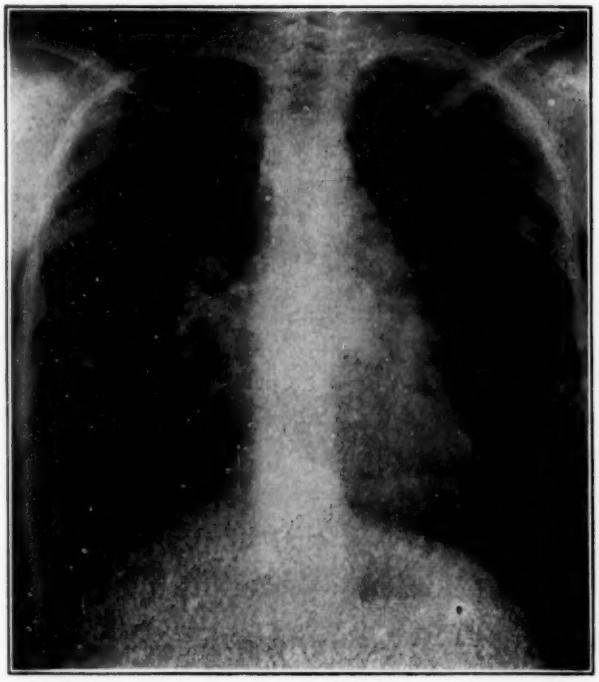

Fig. 2.—D.H. Six days later, showing considerable clearing of infiltrates under antibiotics, digitalis and Meticorten.

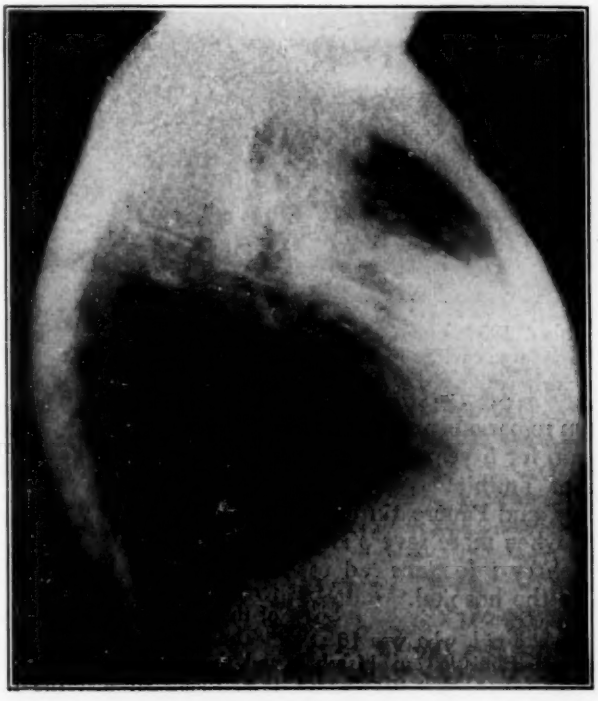

Fig. 3.—Lateral view of same patient at time of second film, showing marked emphysema and dense infiltration at lung roots.

This girl's course, then, is typical of cystic fibrosis of the pancreas with severe recurring respiratory infections ever since early childhood. A unique feature in this patient was the development of atopic allergic manifestations: nasal polyps at age 8, pollen hay fever at age 11, and asthma at 16. Following her third polypectomy and exenteration of the antra at age 14, symptoms of the disease had been remarkably controlled by desensitization for 5 years, periodic administration of antibiotics, corticosteroids, vitamins, and Pancreatin until the fall of 1957, when more severe and persistent pulmonary infections led to her admission to the hospital.

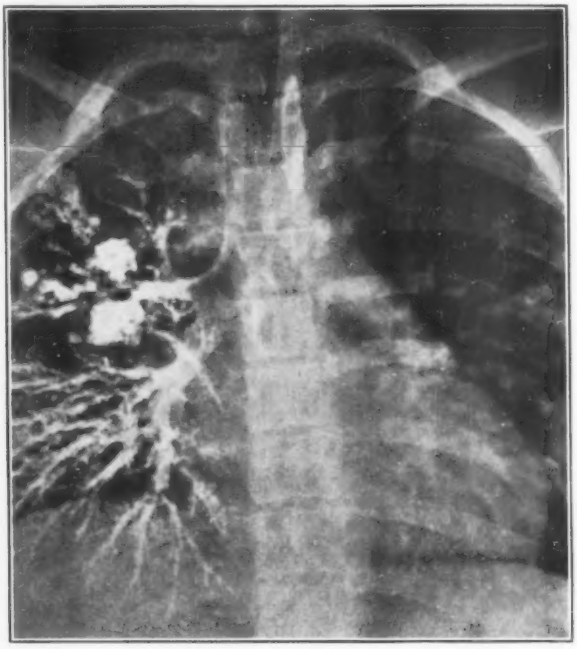

Fig. 4.—B.G. October, 1958, bronchogram immediately after the injection of dye, showing large cavities in a segment of the right upper lobe.

CASE 2. B.G., a white girl, who was 16 at the time of her last admission in March, 1959, had been seen for the first time with Dr. Palmer Futcher 2 years before. Patient gave a history of developing eczema, pollen hay fever and nasal polyps at the age of 7. Asthma developed at age 16 (Table 3). Intracutaneous tests were positive to pollens, other inhalants and foods. During the ensuing years several respiratory infections, presumably pneumonia, had occurred. Her first admission to the Johns Hopkins Hospital, several years ago, was for drainage of infected sinuses, but in spite of this procedure she continued to have a cough productive of purulent sputum. Roentgenograms in 1957 showed slight infiltrations in both upper lobes, but all tests were negative for tuberculosis. A bronchogram in 1957 was read as normal, but in October, 1958, because of a persistance of symptoms, the study was repeated, and by inserting a catheter into the right upper lobe bronchus, a multilocular cavity was demonstrated in the posterior segment of that lobe (Figs. 4 and 5).

The fecal fat was found to be increased, and this, together with the pulmonary findings, suggested that she might have cystic fibrosis of the pancreas. The diagnosis was

verified by a chloride level of 90 mEq. per L. in a sweat test, a very high reading. The sputum at this time, and on each occasion before and since, showed a heavy growth of a coagulase-positive staphylococcus, which was resistant to penicillin, but sensitive to tetracycline, erythromycin, and Chloramphenicol. Under cover of the first two antibiotics a segmental resection was done by Dr. James Cantrell. Microscopic sections showed extensive bronchiectatic changes. The postoperative course was uncomplicated but she was readmitted 2 months later, at which time bronchiectasis was demonstrated in the anterior segment of the left upper lobe. This segment was resected in January, 1959, but on this occasion the postoperative course was nearly terminal, being complicated by a bronchopleural fistula and an empyema. Hydrocortisone intravenously seemed to play a major role in tiding the patient over this most critical phase of the illness. A lobectomy and partial thoracoplasty were required to bring the condition under control and, except for a staphylococcal abscess of the chest wall, she has remained remarkably well ever since. Further laboratory studies confirming the diagnosis of cystic fibrosis were a repeat sweat test which showed a chloride value of 95 mEq. per L., a low serum carotene level and, on duodenal drainage, a low lipase and no trypticase activity. This patient's course, on the whole, has been much milder than that of the first and we are hopeful, now that the areas of suppuration have been removed, that she may be able to lead a life that is nearly normal.

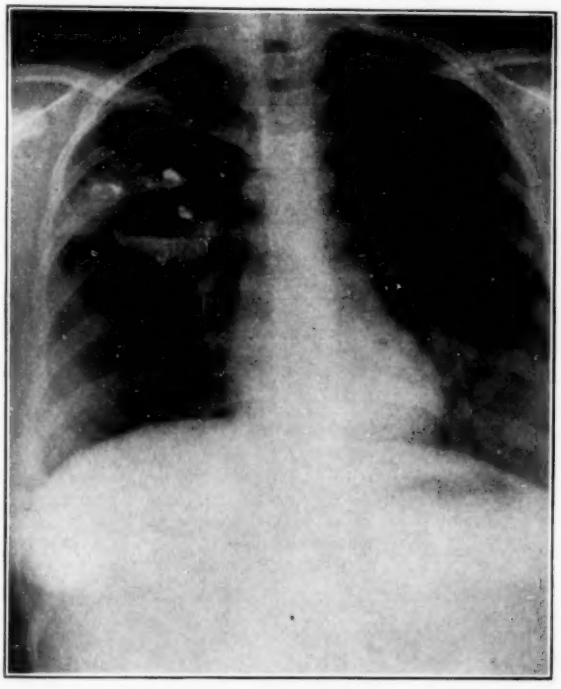

Fig. 5.—B.G., after evacuation of most of the radio-opaque material. Two cavities are demonstrated, one of which has a fluid level.

The clinical and laboratory findings that seem to be of major importance from the standpoint of diagnosis of cystic fibrosis of the pancreas are summarized in Table 1.

ALLERGIC MANIFESTATIONS. The 2 patients whose histories have just been given presented typical allergic manifestations: allergic rhinitis, nasal polyps, and asthma with characteristic

wheal-erythema skin reactions of the immediate type. Treatment was directed, at first, toward the allergic conditions, and the nature of the fundamental disease was temporarily overlooked. Further study of the allergic aspects of this disease is well illustrated by a recent study by Van Metre *et al.*[16] who analyzed a large series of cases of cystic fibrosis (including the 2 patients just described) at the Johns Hopkins Hospital. The authors found a relatively high incidence of atopic allergic conditions, particularly, in the older children, where 8 of 14 patients over 11 years of age were shown to be allergic. The data on the incidence of these allergic manifestations and the results of skin tests are brought out in detail in Tables 2 and 3.

TABLE 1.—ORGANS MOST COMMONLY INVOLVED CORRELATED WITH THE USUAL CLINICAL AND LABORATORY FINDINGS.

Areas Involved	*Clinical and*	*Laboratory Features*
Pancreas	Steatorrhea	Stool fat Enzyme abnormalities
Upper Resp. Tract	Sinusitis	Cultures
Lungs	Bronchopneumonia Bronchiectasis Asthma Emphysema	Cultures Bronchograms Functional studies
Liver	Hepatomegaly Portal hypertension	Liver function tests
Sweat glands	Salt depletion	Increased excretion of Na and Cl
Mucous glands	Changes in bronchi, pancreas, etc. (?)	Possible role in pathogenesis

The frequent association of asthma and cystic fibrosis have been commented on in previous reports (di Sant 'Agnese *et al.*[6], Glaser[9] Sherman and Kessler[13]), and many feel that there is a pathogenetic relationship: the thick mucus, which is characteristic of the disease, leading to obstruction of the small bronchi throughout the lungs. This seems to be a logical concept which might help explain the progressive nature of the condition which is so resistant to treatment, leading to severe emphysema, bronchiectasis and right heart failure. In addition, as this study reveals, the development of the atopic form of rhinitis and asthma represents an additional hazard, aggravating or actually "triggering" some of the pulmonary infections, thereby increasing tissue reaction and damage.

There is, of course, no specific therapy, but each case presents special therapeutic problems, and treatment must be adjusted to the individual patient. Some of the measures most often found useful are: bronchodilators, pancreatic enzymes, all the fat-soluble vitamins, and whatever antibiotics are found indicated by a study of the sputum at the time of an acute infection. If allergic rhinitis and asthma of the atopic type occur, desensitization and avoidance of significant antigens should be observed. Corticosteroids intermittently at first, and continuously during the past 2 years appear to have been efficacious in the first patient described, and their use in asthma, whenever it occurs, in these patients may well be of value.

The prognosis is poor on the whole

TABLE 2.—EVIDENCE OF CYSTIC FIBROSIS IN 14 PATIENTS WHO WERE 11 YEARS OF AGE OR OLDER.

	Number	*Per cent*
Total Number	14	100
Family history of cystic fibrosis	5	36
Abnormal stools	14	100
Pancreatic enzyme deficiency demonstrated	13	93
Rectal prolapse	3	21
Meconium ileus	2	14
Respiratory disease symptoms	14	100
Pulmonary infiltrate	14	100
Emphysema	14	100
Wheezing	9	64
Clubbing of fingers	13	93
Rhinitis	14	100
Failure to thrive	14	100
Sinus roentgenograms obtained	8	
Roentgenographic evidence of sinusitis	8	
Sweat chloride		
Not measured	6	
Normal	1	
Elevated	7	
Died of cystic fibrosis	4	
Necropsy evidence of cystic fibrosis	3	
No necropsy	1	

TABLE 3.—CLINICAL DATA ON EIGHT PATIENTS 11 TO 20 YEARS OF AGE WITH CYSTIC FIBROSIS OF THE PANCREAS WHO HAD EVIDENCE OF ATOPIC ALLERGY

	D.H.	*R.S.*	*M.R.*	*S.P.*	*K.C.*	*B.G.*	*C.N.*	*B.M.*
Age in years								
Last observation	19	18	20	18	11	16	12	12
Death	Liv.	Liv.	Liv.	Liv.	11	Liv.	12	Unk.
Family history of allergy								
Parents or siblings	0	+	0	0	+	0	0	0
Other than parents or siblings	+	+	0	0	+	0	0	0
Age in years at onset of								
Asthma	16	15	12	1	2	16	–	1
Rhinitis	4	3	5	1	1	–	1	1
Nasal polyps	10	9	12	–	10	7	6	8
Hay fever	11	14	–	10	–	7	–	–
Eczema	–	–	–	3/12	–	7	–	–
Urticaria	–	14	5	0	–	–	–	–
Respiratory symptoms near animals	14	–	5	10	–	7	–	–
Intracutaneous tests								
Pollens	+	+	neg.	+	+	+	ND*	ND
Other inhalants	+	+	+	+	+	+	ND	ND
Foods	ND	ND	neg.	ND	ND	+	ND	ND
Bacteria	+	+	+	+	+	neg.	ND	ND

*Not done

and determined, for the most part, by the severity of the pulmonary complications, which may be aggravated by the development of atopic respiratory disturbances.

Summary. (1) Two cases of cystic fibrosis of the pancreas in young adults have been reported in detail. The progress of the condition in these 2 individuals illustrates the fact that the manifestations of the disease may vary greatly.

(2) Consideration of a fairly large series of patients with cystic fibrosis indicates that a relatively high proportion develops allergic manifestations of the atopic type, the reason for which is not clear, but which may be related to the basic pathophysiology of the underlying disease.

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SUMMARIO IN INTERLINGUA

Manifestationes Pulmonar e Allergic de Fibrosis Cystic del Pancreas

1. Duo casos de fibrosis cystic del pancreas es reportate in detalio. Le patientes esseva juvene adultos. Le progresso del condition in le 2 casos illustra le facto que le manifestationes del morbo pote variar grandemente.

2. Le examine de un satis extense serie de patientes con fibrosis cystic del páncreas indica que un relativemente alte proportion disveloppa manifestationes allergic del typo atopic. Le ration pro iste facto non es clar, sed illo es possibilemente relationate al pathophysiologia del morbo subjacente.

COMPARISON OF THREE NEW ANTIHISTAMINICS WITH PARABROMDYLAMINE MALEATE

By Jerome Miller, M.D.

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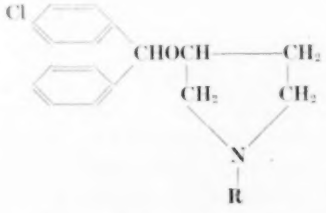
Relatively minor changes in the chemical structure of an antihistaminic compound result in new substances having different pharmacologic properties. For example, increased antihistaminic potency has been realized in the prophenpyridamine (2-[α-(2-dimethylaminoethyl)-benzyl]-pyridine) series by introduction of a chlorine atom (chlorprophenpyridamine) or a bromine atom (parabromdylamine) into the para position of the benzene nucleus (Sperber *et al.*[10]).

Recently, a new series of antihistaminic compounds has been synthesized which involves more extensive structural changes (Lunsford *et al.*[6]). These substances are benzhydryl ethers of the 3-pyrrolidinol system, the most potent of which have halogen substitution in one benzene nucleus. Pharmacological studies of these compounds resulted in the selection of three (AHR-209, AHR-211, and AHR-224) for clinical evaluation. The formulas of these compounds are as follows:



R = CH_3 — AHR-224
R = C_2H_5 — AHR-211
R = iso-C_3H_7 — AHR-209

All of the antihistaminic compounds used in the study were furnished as maleate salts; 12.4 mg. of the maleate salts of AHR-209, AHR-211 and AHR-224 contain the same amount of the free base as 10 mg. of the HCl salts used in previously reported studies (Lunsford *et al.*[6]).

The present investigation was designed to evaluate and compare these new antihistaminic agents with parabromdylamine maleate, a potent antihistamine with known pharmacological properties (Robins Company[8], Dann, Brown and Ruchocki[1], Fuchs and Maurer[2], Horstman[3], Kreindler, Ghory and Bernstein[4], Lipman[5], Thomas[11]).

Clinical design. Most of the patients in this study had been observed over months or years and had been receiving specific hyposensitization and palliative measures as needed. Previous treatment was continued with the exception that the four compounds were substituted in rotation for the antihistaminic compound previously employed. New patients received injections of buffered saline solution in lieu of specific hyposensitization to rule out psychological responses and to standardize the method as much as possible.

The study employed the double-blind technique in which the drugs were identified as A, B, C, and D. The

patients received each drug for a period of 6 days followed by a one-day rest period before the next drug was started. In order to minimize bias that may be introduced by differences in extraneous conditions such as weather, pollen concentration, temperature, and the like, an approximately equal number of patients was taking each drug each week. Thus, changing environmental conditions did not unduly influence the evaluation of any one drug. Throughout the study the patients were asked to observe the effectiveness of the various compounds and record their preference. These preferences were later compared with the objective findings of the investigator. All data were collected and collated by a disinterested individual before the lettered compounds were identified.

Material and Method. A series of 109 patients was obtained from private practice and the allergy clinics of the Skin and Cancer Hospital, Union Health Center and A.F.L. Medical Center. Of the 92 patients who completed the series, 62 were women and 30 men, ranging in age from 8 years to 72 years. Subjective improvement was indicated by fewer nasal symptoms, less dyspnea, wheezing and cough, and subsidence of itching and hives. Objective improvement was determined by examination of the nose, skin, and chest.

All patients in the study were aware that they were taking part in the evaluation of new antihistamines and each was instructed to indicate his preference on a weekly check list that was provided. A careful note was made of other drugs taken by the patient; extraneous environmental, home and social factors, pollen concentrations; temperature; humidity; and wind velocity. Each patient was observed by the investigator on four or more occasions over a period of 4 weeks. The patient returned to the office weekly for the following week's supply of 25 capsules which were allotted according to a randomized schedule. Each week's supply was enough for 6 days of medication and a 24-hour drug-free period. Since the capsules were identical in color, shape, and size, neither the patient nor the investigator was able to identify them except by code number.

A fixed dosage of 49.6 mg. of the experimental compounds and 16 mg. of parabromdylamine was administered to all patients in the study. The larger dosage of the experimental compound increased the probability that a therapeutic effect would be observed and permitted an evaluation of the pharmacologic action of the drugs. It also enabled the investigator to observe any side effects that might occur through magnification of their intensity. It was recognized, however, that the use of a fixed dosage schedule would furnish too much medication for some patients and not enough for others.

The therapeutic response to medication was graded numerically from 3 to 0, as follows:

Excellent relief was graded 3 and interpreted as almost complete absence of symptoms and no side effects.

Good was designated as 2 and indicated negligible complaints and occasional side effects.

Fair was coded as 1 and indicated only slight symptomatic relief and increased side effects.

Poor was coded as 0 and meant no relief or marked adverse reactions, or both.

Results. The results observed in 92 patients are recorded in Table 1. Statistically, parabromdylamine in 4-mg. doses and AHR-224 in 12.4-mg. doses appeared to be equal in antihistaminic action and superior to the other two compounds. AHR-209 and AHR-211 in 12.4-mg. doses were less effective than the other two and were not statistically different in effectiveness from each other.

In general, there was remarkably close correlation between the investigator's objective evaluation of the drug's action and the patient's choice of the most effective drug. Of the 92 patients, 81 indicated a preference for one or more drugs. In this group of patients, there was a 94% agreement between the patient's evaluation and the investigator's.

SIDE EFFECTS. The two most frequently-reported side effects in this study were drowsiness and dryness of the nose and throat. Other side effects were

varied and in most cases were not excessive. Two patients developed a possible hypersensitive reaction in the form of a macular nonpruritic eruption which subsided on continued medication. The overall incidence of side effects was 21.5%. Forty-six of the 92 patients experienced no side effects to any of the compounds and no signs of clinical toxicity were noted in any of the patients. Since previous investigators had already reported on the absence of toxic reactions, laboratory studies were not performed.

TABLE 1.—PATIENT RESPONSE TO ANTIHISTAMINES, ACCORDING TO ALLERGIC MANIFESTATION

Symptoms	*Cases*	*Dose*	*Results*				*Patients with One or More Side Effects*
			Exc.	*Good*	*Fair*	*Poor*	
Perennial hay fever							
AHR-209	63	49.6 mg./day	11	27	13	12	13
AHR-211	63	49.6 mg./day	7	25	20	11	15
AHR-224	63	49.6 mg./day	25	15	13	10	8
Dimetane	63	16.0 mg./day	21	22	15	5	14
Skin manifestations							
AHR-209	17	49.6 mg./day	2	3	5	7	6
AHR-211	17	49.6 mg./day	0	4	5	8	5
AHR-224	17	49.6 mg./day	3	9	2	3	6
Dimetane	17	16.0 mg./day	5	4	3	5	3
Bronchial asthma							
AHR-209	9	49.6 mg./day	0	4	2	3	2
AHR-211	9	49.6 mg./day	1	1	3	4	1
AHR-224	9	49.6 mg./day	4	3	0	2	1
Dimetane	9	16.0 mg./day	2	3	2	2	4
Miscellaneous							
AHR-209	3	49.6 mg./day	0	2	1	0	0
AHR-211	3	49 6 mg./day	1	0	1	1	1
AHR-224	3	49.6 mg./day	1	1	1	0	0
Dimetane	3	16.0 mg./day	0	0	2	1	0
Overall Effectiveness:							
AHR-209	92	49.6 mg./day	13	36	21	22	21
AHR-211	92	49.6 mg./day	9	30	29	24	22
AHR-224	92	49.6 mg./day	33	28	16	15	15
Dimetane	92	16.0 mg./day	28	29	22	13	21

Discussion. In this series of patients, the results obtained in those with seasonal and perennial hay fever and those with urticaria were especially gratifying. The patients with seasonal and perennial hay fever reported a satisfactory suppression of oculonasal symptoms, accompanied by relief of itching and tearing with diminished sneezing and nasal obstruction. The patients with urticaria stated that the hives subsided and the pruritus was relieved so that they could work and sleep in comfort.

The therapeutic response was usually obtained within 30 minutes after ingestion of the capsules and continued for 6 to 8 hours. During the course of the study, a number of patients found that early morning nasal symptoms were considerably reduced when the medication was taken every 6 hours,

day and night, rather than only in the daytime hours. This observation enabled many patients to take full advantage of the antihistaminic properties of these compounds.

The investigator's ratings of the patient's response to medication were transformed into *rankits* for purposes of normalization and the analysis of variance is summarized in Table 2.* No attempt was made to statistically analyze the patient's ratings of the drugs.

TABLE 2.—ANALYSIS OF VARIANCE

Source	*Degrees of Freedom*	*Sum of Squares*	*Mean Square*	*F*
Between subjects	87	69.243	.796	2.14†
Between drugs	3	11.504	3.835	10.33‡
D versus A	1	.007(26)	.007	.02
B versus C	1	.339	.339	.91
A & D versus B & C	1	11.158	11.158	30.06‡
Error	261	96.879	.371	
Total	351	177.625		

†$P \leqq 0.01$
‡$P \leqq 0.001$

We see from these data that drugs D and A could not be discriminated between; nor could drugs B and C be so discriminated. However, the difference between the "good" drugs, A and D, and the "poor" drugs, B and C, was highly significant ($P \leqq .001$). The mean scores are given below for males and females separately and also for all subjects. Since the sex of the patient was not recorded on several charts, the scores of these patients appear only under "All subjects."

TABLE 3.—MEAN EFFECTIVENESS OF DRUG ACCORDING TO SEX (IN RANKIT UNITS)

	A	*B*	*C*	*D*
Male	1.28	1.00	.90	1.19
Female	1.26	.93	.85	1.30
All subjects	1.25	.95	.86	1.26

As the response according to sex appeared to be quite consistent, the analysis of variance was not extended to cover the sex differences.

Although the incidence of side effects was higher than may be expected from similar antihistamines, an explanation may be found in the high dosage schedule used. All patients received the same daily dosage, rather than an individualized dosage based on the intensity of symptoms and the therapeutic response. Undoubtedly, some of the side effects may have been lessened or eliminated if a varied dosage schedule had been used. On the other hand, half of the 92 patients did not complain of any side effects. In fact, the dosage of a few patients who obtained negligible benefit at the fixed dosage was increased to 62 mg. and 74.4 mg. a day without the occurrence of appreciable side reactions. As with other antihistaminic preparations, a minimum dose of the experimental compounds caused sedation in an occasional patient.

The observations regarding the superiority of AHR-224 (Compound D) are at variance with those of other investigators (MacLaren[7], Robins Com-

*The statistical analyses reported in this paper were performed by Malcolm E. Turner, Ph.D., Associate Professor, Department of Biophysics and Biometry, Medical College of Virginia, Richmond.

pany[9]), and may have been due to higher dosages employed in the present study. When given at a dosage of 49.6 mg. a day, AHR-224 is a potent antihistaminic agent and appears to be equally effective as 16 mg. of Dimetane.

AHR-224 may be used in much the same manner as other antihistaminic agents to suppress the symptoms of allergic disorders. As such, it is a useful agent, but does not replace specific diagnosis and other necessary management of allergic disorders.

Summary. Four compounds A, B, C, and D, were evaluated in a double-blind study involving 92 patients with a variety of allergic disorders. Capsules of the experimental compounds contained 12.4 mg. each and the parabromdylamine maleate capsule contained 4 mg. of the antihistamine. Previous pharmacologic studies indicate that these compounds possess potent antihistaminic properties with few undesirable side effects. Clinical observations by previous investigators proved their effectiveness in the management of allergic states.

The present study showed AHR-224 (compound D) to be as effective as parabromdylamine maleate (compound A). The superiority of parabromdylamine and AHR-224 over the other two compounds may have been a manifestation of dose response at the dosage level used in the present study. The incidence of side effects to AHR-224, however, was only 16.3%, compared with an average incidence of 23.2% to the other three compounds. Drowsiness and dryness of the nose and throat seemed to be the most frequent complaints.

A comparison of results as reported by the investigator and the patients showed very good correlation of objective and subjective findings. When the daily dosage of 4 capsules was equally spaced so that one capsule was taken every 6 hours, the patients obtained maximum relief and seemed to be more effectively relieved of early morning discomfort.

Conclusion. AHR-224 has sufficient antihistaminic properties and a low enough incidence of undesirable side effects to justify its use for the symptomatic treatment of allergic disorders. In this clinical study it was superior to the other two experimental compounds tested.

ACKNOWLEDGMENT: The compounds used in this study were furnished through the courtesy of the A. H. Robins Co., Inc., Richmond, Virginia.

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SUMMARIO IN INTERLINGUA

Comparation Inter Tres Nove Antihistaminicos e Maleato de Parabromdylamina

Quatro compositos—identificate como A, B, C, e D—esseva evalutate in un studio bisocculte con 92 patientes suffrente de un varietate de disordines allergic. Le capsulas experimental a B, C, e D contineva 12,4 mg cata un de AHR-209 o AHR-211 o AHR-224. Le capsulas designate como A contineva 4 mg de maleato de parabromdylamina. Previe studios pharmacologic indica que iste compositos possede potente proprietates antihistaminic con pauc indesirabile effectos lateral. Observationes clinic per previe investigatores provava lor efficacia in le tractamento de statos allergic.

Le presente studio monstrava que AHR-224 (composito D) es tanto efficace como maleato de parabromdylamina (composito A). Le superioritate de parabromdylamina e de AHR-224 in comparation con le altere duo compositos esseva possibilemente un manifestation del responsa dosificatori al nivello de dosage usate in iste studio. Tamen, le incidentia de effectos lateral in AHR-224 esseva solmente 16,3 pro cento in comparation con le incidentia medie de 23,2 pro cento in le altere tres compositos. Somnolentia e siccitate del bucca e del gurgite pareva esser le plus frequente gravamines.

Un comparation del resultatos reportate per le investigator e per le patiente individual revelava un correlation multo bon del constatationes objective con le constatationes subjective. Quando le dosage diurne de quatro capsulas esseva administrate a equal intervallos de tempore de maniera que un capsula esseva ingerite omne sex horas, le patientes obteneva un maximo de alleviamento. Lor alleviamento ab disconforto in le prime matino esseva apparentemente plus efficace.

Le conclusion es que AHR-224 possede sufficientemente forte proprietates antihistaminic e un sufficientemente basse incidentia de indesirabile effectos lateral pro justificar su uso in le tractamento symptomatic de disordines allergic. In le presente studio clinic illo esseva superior al altere duo compositos experimental testate.

SUMMARIO IN INTERLINGUA

(See page 487 for original article)

Le Effectos Cardiovasculo-Respiratori de Un Nove Derivato Xanthinic in Chronic Emphysema Pulmonar e in Stenosis Mitral

Dece-un casos de "pur" stenosis mitral e 8 casos de avantiate emphysema pulmonar esseva studiate durante catheterismo, in stato de reposo, e 30 minutas post le administration intravenose de 0,1 a 0,2 g del nove derivato xanthinic, Ro 1-8239. Le droga augmenta le ventilation alveolar; illo reduce le spatio morte physiologic, le pCO_2 arterial, e le proportion de spatio morte physiologic a volumine de aere currente; illo augmenta le pH de sanguine arterial. Iste alterationes es interpretate como action super le circulation pulmonar, associate—probabilemente—con bronchodilatation.

Le droga produceva un declino del tension systemic e del tension pulmonar al fin de 15 e de 30 minutas. Illo reduce omne resistentias e augmenta le rendimento cardiac. Iste alterationes resulta de vasodilatation, tanto systemic como etiam pulmonar.

OBSERVATIONS CONCERNING THE SIGNIFICANCE OF FATTY AND FIBROUS TISSUE IN NEEDLE BIOPSIES OF THE LIVER

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The significance of fatty change of the liver and its relationship to Laennec's cirrhosis have been the subject of much controversy. Although the presence of fatty change in cirrhosis was noted by Addison[1] in 1836 and the high fat content in the livers of alcoholics was cited 12 years later by Rokitansky[27], it was not until the discovery of the lipotrophic effect of choline by Best and associates[2,3,4] that great interest in the fatty liver was stimulated. In 1934 MacLean and Best[23] described the development of fatty change and early fibrosis of the livers in dogs fed choline-deficient diets. This observation was followed by the recognition of cirrhosis in dogs by Chaikoff and Connor[7] and in rats by György and Goldblatt[14] when these animals were maintained on choline deficient diets. In 1938 Connor[9] reviewed the clinical and necropsy findings of a series of patients who died of alcoholism and concluded that fatty change, with or without fibrosis, and cirrhosis represented progressive stages of the same disease. The concept that fatty change is essential to the development of cirrhosis has received support from Chaikoff, Connor and Biskind[8], Himsworth[17], and Hartroft[15,16] but has been refuted by others (Davies[10], Dible[11]). Much of the information concerning the significance of the fatty liver in man has been obtained from the analysis of necropsy material and needle biopsies. However, it is to be noted that many of the latter were not sequential for any particular individual. In 1948 Buck[6] indicated that serial biopsies in patients with early cirrhosis might help elucidate the natural history of this disease. Although many studies have been reported in which short term interval biopsies were performed demonstrating the effect of therapy on the fat content in the liver (Buck[6], Eckhardt *et al.*[12], Kessler, Seife and Lisa[21,29], Phillips, Gabuzda and Davidson[24], Volwiler, Jones and Mallory[31]) only two reports (Leevy *et al.*[22], Schiff, Gall and Young[28]) dealing with long-term serial studies to determine the histologic changes occurring in patients known to have fatty livers are recorded. The excellent survey reported by Leevy and associates[22] contained 9 instances of portal cirrhosis, 2 of fatty change with portal fibrosis, and 2 of fatty change in a group of chronic alcoholics who had previously been shown to have fatty change in the liver 1½ to 5 years previously. Schiff, Gall and Young[28] studied a patient during a 10-year period with liver func-

tion studies and hepatic needle biopsies. Many of the latter revealed varying degrees of fatty change, but the final biopsy demonstrated morphologic changes similar to early nutritional cirrhosis.

In order to gain a better understanding of the significance of fatty change and fibrosis of the liver as observed in needle biopsies of this organ we have performed subsequent studies on a group of patients in whom this diagnosis was established by this method.

Methods and Procedures. The clinical records of 91 patients at the Pittsburgh Veterans Administration Hospital having hepatic needle biopsies diagnosed as either fatty change or fatty change with portal fibrosis during the years 1955 to 1957 were reviewed. All but 16 were excluded from subsequent study because they were lost for follow-up or succumbed because other hepatic disease such as metastatic carcinoma became manifest. These 16 patients were subjected to needle biopsy of the liver with a Vim Silverman needle utilizing the transthoracic approach of Iversen and Roholm[18]. The tissue obtained was fixed in Zenker's acetic fluid and sections were stained with hematoxylin-eosin and a modified trichrome stain. The degree of fatty change, as evidenced by vacuolation of the cytoplasm of the liver cells, was evaluated by two observers as either mild, moderate, or severe (Figs. 1*A*, 1*B*, 1*C*). The criteria employed in this classification were similar to those of Billing and associates[5]. Spotty cytoplasmic vacuolation of the liver cells corresponding to 20 vacuoles per low power field was considered as slight fatty change. Vacuolation of one-third of the cells of a biopsy specimen corresponding to about 60 vacuolated cells per low-power field was called moderate fatty change. Specimens in which the cytoplasmic vacuolation was greater were classified as severe fatty change. Cirrhosis of the liver was diagnosed only when definite nodule formation produced by connective tissue septae was evident. The presence of increased connective tissue in the absence of nodule formation was designated as portal fibrosis. An attempt to evaluate the dietary and alcoholic habits was made by a careful review of the patient's medical and social history. Assuredness of abstinence from alcohol was considered valid when individuals exhibited weight gain in the absence of anasarca or edema, presence of normal liver function tests and a confirmed history of such a practice. The following tests of liver function were performed: bromsulfalein test (Caebler), cephalin flocculation test (Hanger), thymol turbidity (MacLagen), serum protein (Biuret), and prothrombin time (Simplastin method*).

Results. The clinical and histologic findings are listed in Table 1. Table 2 contains the essential biochemical determinations. The interval between histologic examinations of the liver ranged from one year and one month to 5 years. The average interval was 2.4 years. The estimated quantity of fat in the liver of 6 patients (Nos. 3, 4, 10, 12, 13, 15) was evaluated as remaining constant. Patients Nos. 10 and 15 denied any history of alcoholism, whereas patients Nos. 3, 4 and 12 stated they had stopped drinking alcoholic beverages after the first liver biopsy. Patient No. 13 was classified a chronic alcoholic. There was a decrease in the fat content of the livers in patients Nos. 2, 9 and 14. Patient No. 14 claimed to have corrected his alcoholic problem, and patients Nos. 2 and 9 denied any use of alcohol. The portal fibrosis demonstrated in patient No. 8 remained constant. Six patients (Nos. 1, 5, 6, 7, 11 and 16) demonstrated an increase in either or both the fat content and connective tissue of their livers. All these patients were chronic alcoholics except patient No. 7 who claimed to have stopped drinking 14 years previously. Laennec's cirrhosis was demonstrated in patient No. 6. Initially this man had been admitted to the hospital in 1956 for bizarre abdominal complaints. The only positive findings after an extensive investigation at that time was an enlarged liver which was demonstrated to contain a moderate amount of fat by needle bi-

*Warner-Chilcott.

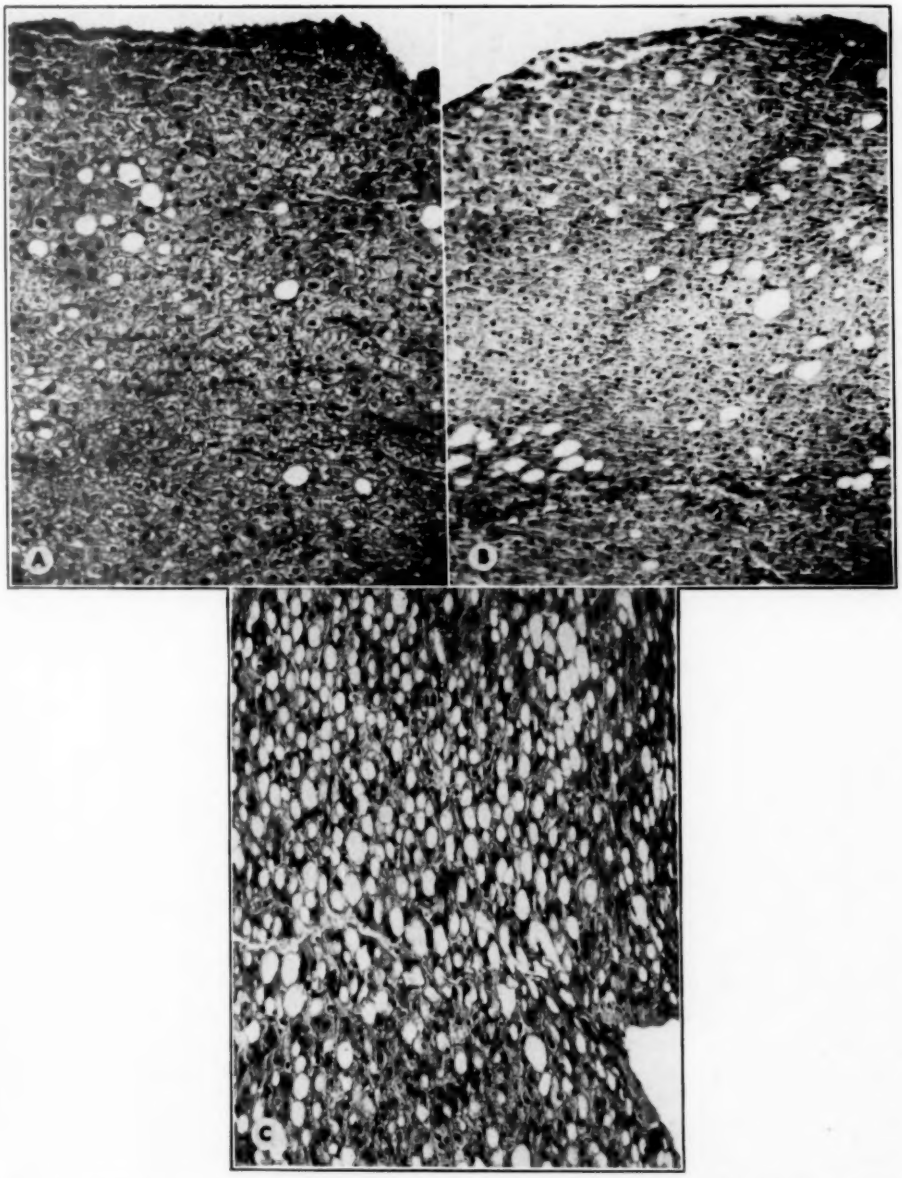

Fig. 1.—Stages of fatty change in the liver. *A*, slight fatty change characterized by spotty vacuolation of the cytoplasm of the hepatic cells; × 110. *B*, moderate fatty change showing cytoplasmic vacuolation of one-third of the cells; × 110. *C*, severe fatty change characterized by cytoplasmic vacuolation in more than one-third of the cells; × 110.

TABLE 1.—CLINICAL AND HISTOLOGIC FINDINGS

Patient	*Age*	*Interval*	*Alcoholic History*	*Nutrition*	*Associated Disease*	*Liver Biopsy*	
						Initial	*Repeat*
1	46	5.00	Chronic	Poor	Arteriosclerosis	Fatty change, moderate	Portal fibrosis and bile duct proliferation
2	59	3.75	None	Adequate	Rheumatoid Arthritis and Tuberculosis	Fatty change, slight	Normal liver
3	59	3.12	Abstained	Adequate	None	Fatty change, slight	Fatty change, slight
4	50	3.91	Abstained	Adequate	Diabetes Mellitus	Fatty change, slight	Fatty change, slight
5	45	2.50	Chronic	Adequate	None	Portal fibrosis and inflammation	Fatty change and portal fibrosis
6	41	2.91	Chronic	Adequate	Diabetes Mellitus	Fatty change, moderate	Cirrhosis of liver Laennec's type
7	46	2.33	None	Adequate	Diabetes Mellitus	Fatty change, slight	Fatty change, moderate
8	52	2.33	Chronic	Adequate	Diabetes Mellitus Bronchopneumonia	Portal fibrosis	Portal fibrosis
9	48	1.66	None	Adequate	None	Fatty change, moderate	Normal liver
10	59	1.66	None	Poor	None	Fatty change, slight	Fatty change, slight
11	58	2.12	Chronic	Poor	None	Fatty change, moderate	Fatty change, severe
12	68	1.08	Abstained	Adequate	Obesity	Fatty change, severe and Portal Fibrosis	Fatty change, severe
13	38	1.75	Chronic	Poor	None	Fatty change, severe	Fatty change, severe
14	46	1.75	Abstained	Adequate	None	Fatty change, slight	Normal liver
15	38	1.83	None	Poor	None	Fatty change, moderate	Fatty change, moderate
16	41	1.91	Chronic	Poor	Discoid Lupus	Fatty change, moderate Portal Fibrosis	Fatty change, severe

opsy (Fig. 1*B*). When he was readmitted to the hospital for this study he was in metabolic acidosis due to diabetes mellitus. A needle biopsy of his liver then showed cirrhosis of the liver, Laennec's type (Fig. 2). The bromsulfalein test was the only abnormal biochemical determination at the time of the second liver biopsy in this patient. Diabetes mellitus was present in 3 other patients of this group. Their subsequent liver biopsies failed to reveal any change from that noted previously except for a moderate increase in the fat content in one.

Fig. 2.—Second hepatic needle biopsy from patient No. 6 revealing changes of cirrhosis, Laennec's type. This biopsy was obtained 2.9 years following an initial biopsy which revealed moderate fatty change (Fig. 1*B*).

It was of interest that the results of the tests of liver function, particularly the bromsulfalein test, correlated well with sociologic and clinical evidence of alcoholic abstinence, reverting to normal in one case.

Discussion. The results of this study indicate that a variety of conditions are associated with fatty change of the liver. Alcoholism was the most frequent cause of this alteration. Obesity (Zelman[32]), diabetes mellitus (Jaques[19]), and chronic infection (Popper and Schaffner[25]) were also noted. Laennec's cirrhosis was subsequently evident in one of the 4 cases of diabetes mellitus with initial needle biopsies revealing fatty or fibrous change in the liver. This is of interest since it has been noted that cirrhosis is rarely associated with diabetes mellitus (Joslin *et al.*[20]). Frankel, Asbury and Baker[13] questioned the pathogenetic significance of diabetes in cirrhosis and indicated that cirrhosis occurring in diabetic patients usually had another more acceptable etiology. This was apparent in our patient since he was considered as a chronic alcoholic. Only one other patient exhibited changes approaching the his-

tologic features of cirrhosis. This man was a chronic alcoholic with poor nutrition who showed portal fibrosis with bile duct proliferation 5 years after the original liver biopsy demonstrated only moderate fatty change. The lack of absolute nodule formation, however, prevented a definite diagnosis of cirrhosis.

It is apparent that the follow-up interval in the remaining cases studied may not have been sufficiently long to allow for a transition to cirrhosis to become evident. It should be noted, however, that Hartroft[16] has indicated that the presence of fat in the liver even over a prolonged period does not necessarily result in fibrosis. He considered an accelerated accumulation of fat to be more significant in the pathogenesis of portal fibrosis. On the other hand, Popper, Szanto and Elias[26] concluded from their studies based on three dimensional reconstruction and geometrical analysis of livers in various developmental stages of cirrhosis that fat played only a minor role in the development of fibrosis. They considered parenchymal necrosis with subsequent inflammatory change in the portal areas and stress fissures which develop between areas of uneven tissue turgor to be the important factors concerned with the formation of fibrous tissue septae. A similar view has been recently expressed by Shorter and Baggenstoss[30]. However, in our study one patient, who had fatty change in the liver and needle biopsy subsequently disclosed Laenenc's cirrhosis 2 years and 11 months later, did not have evidence of cellular necrosis.

Portal fibrosis observed in the initial biopsy from 2 patients was not demonstrated by repeat examination. These findings would indicate that portal fibrosis in these patients was either a focal process or that the biopsy was inadequate. Resolution of the fibrous tissue appears highly unlikely. Seife, Kessler and Lisa[29] demonstrated the inconsistency of revealing fibrotic change in the liver with the needle biopsy technique. Popper and Schaffner[25] estimated that 10% of cirrhosis may not be demonstrated by this tech-

TABLE 2.—BIOCHEMICAL DETERMINATIONS

	Total Protein (Gm.%)		*BSP %*		*Thymol Turbidity (Units)*		*Cephalin Floc. (48 hrs[a])*	
Patient	*I**	*R†*	*I*	*R*	*I*	*R*	*I*	*R*
1	6.7	6.7	4.0	16.0	—	3.5	0	0
2	5.3	7.8	0.0	0.0	17.0	7.4	4+	4+
3	6.9	—	5.0	4.8	—	—	0	–
4	6.5	7.1	4.5	3.5	—	1.0	–	2+
5	7.0	8.0	5.5	13.0	—	1.8	1+	2+
6	6.3	7.7	8.0	35.0	2.4	2.7	2+	2+
7	6.6	7.7	16.0	5.0	2.0	1.3	0	1+
8	6.6	6.9	—	3.0	0.2	1.3	0	0
9	5.8	—	4.0	3.0	0.2	0.2	3+	1+
10	7.2	8.3	3.0	3.0	1.3	—	2+	1+
11	7.1	8.4	13.0	6.5	0.6	—	1+	1+
12	6.8	—	52.0	9.5	1.9	1.8	2+	1+
13	5.9	—	12.0	7.0	—	1.8	0	2+
14	7.6	6.6	26.0	3.0	0.2	1.3	–	2+
15	7.6	7.5	8.5	6.5	5.0	6.6	1+	2+
16	8.6	9.7	17.0	19.0	5.0	2.0	2+	3+

I* Initial Study
R† Repeat Study

nique. Although our case which demonstrated cirrhosis may have been missed by previous biopsy, it appears worthy to note that he had no clinical or biochemical evidence of cirrhosis at the time of initial biopsy. Our own experience would indicate that 10% is too high a value providing the portal and central areas are present for histologic evaluation.

Admittedly an alcoholic history is frequently unreliable. However, in this study a patient was classified as an alcoholic if he obviously consumed excessive quantities of alcoholic beverage. When a former chronic alcoholic claimed to have abstained from alcoholic beverages, he was classified as correcting his alcoholism only when social dependability was demonstrated from the history and definite improvement of the clinical and biochemical examinations were evident. Nutritional status was evaluated from clinical observations, dietary histories, and comparison of body weights on various hospital admissions, excluding weight determinations made during episodes of anasarca. Repeat liver biopsies in 3 of 4 patients who corrected their alcoholism following their initial study, showed no histologic change while the other patient showed normal hepatic histology. It appears significant that the 7 patients classified as chronic alcoholics showed no regression of pathologic change. Their liver biopsies were evaluated as disclosing similar amounts of fat or fibrous tissue or quantitative progression of these alterations. These findings suggest that fatty change may play a role in the pathogenesis of fibrosis and perhaps cirrhosis in individuals who continue their poor nutritional habits, and that proper nutrition and abstinence from alcoholic beverages exert a favorable influence on hepatic histology as well as function. There was no correlation between the liver function tests and the amount of fibrous or fatty tissue change present in the liver biopsies. The bromsulfalein test was the most frequently altered determination, but no correlation between the degree of bromsulfalein retention and histologic change could be made. Two patients whose liver biopsies showed slight fatty change had 16% and 26% retention respectively, while 2 patients with severe fatty change had determinations of 9.5% and 6.5%. It is of interest to note, however, that 4 of the 6 patients who showed an increase in either the fat or connective tissue, or both, of their livers had bromsulfalein retention and were considered alcoholics. Two of the 4 patients who corrected their alcoholism and poor nutrition had marked reductions of the dye retention. The other 2 patients had normal determinations on both admissions. These findings would again indicate a beneficial effect of nutrition and abstinence from alcoholic beverages. The therapeutic implications of these observations are obvious.

Summary. Needle biopsies of the liver and liver function tests were performed on 16 male veterans whose livers revealed fatty change or portal fibrosis, or both, by needle biopsy one to 5 years previously. Seven patients exhibited no change in the fat or fibrous tissue content of their livers, whereas 6 revealed a quantitative increase and in 3 a decrease was observed. In one instance a diagnosis of Laennec's cirrhosis was established. The results of the bromsulfalein test and the degree of fatty and fibrous change within the liver as revealed by needle biopsy appear to be correlated with the patient's alcoholic and nutritional status. It is concluded that these hepatic alterations may be of therapeutic and pathogenetic significance when considered in conjunction with the clinical findings.

ACKNOWLEDGMENT: The authors acknowledge the assistance of Edward Waddell, M.D., who performed the needle biopsies.

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SUMMARIO IN INTERLINGUA

Observationes Relative al Signification de Tissu Grasse e Fibrose in Biopsias Hepatic a Agulia

Biopsias a agulia e tests functional del hepate esseva effectuate in 16 veteranos mascule in qui, inter 1 e 5 annos previemente, biopsia a agulia habeva revelate alteration grasse o fibrosis portal o ambes. Septe patientes monstrava nulle alteration del contento de grassia o tissu fibrose de lor hepates. In 6 un augmento quantitative esseva observate, in 3 un reduction. In 1 caso, le diagnose de cirrhosis de Laennec esseva establite. Le resultatos del test a bromsulfaleina e le grado de alteration grasse o fibrose intra le hepate, como illo es revelate per biopsia a agulia, pare esser correlationate con le stato alcoholic e nutritional del patiente. Es concludite que iste alterationes hepatic es possibilemente de signification therapeutic e pathogenetic quando illos es considerate in conjunction con le constatationes clinic.

PSEUDO-PSEUDOHYPOPARATHYROIDISM

THREE CASES IN ONE FAMILY

By Stanley S. Tanz, M.D.
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Albright *et al.*[1] reported in 1942 on 3 patients with typical blood chemistry findings of hypoparathyroidism (depressed serum calcium and elevated inorganic phosphorus), but showing resistance to the phosphaturic response expected from the intravenous administration of parathyroid extract (Ellsworth-Howard test). A biopsy revealed normal parathyroid glands in one of these patients. The patients were round-faced, short and stocky and exhibited some or all of these symptoms: brachydactylia, convulsions, laryngospasm, tetany, mental retardation, and dental defects. Tetany was the presenting symptom in almost all of the 40 cases presented to date, and calcifications of the basal ganglia, ossifications in the subcutaneous tissues, cataracts, and bony abnormalities such as exostoses, thickening of calvaria, bowing of bone, and syndactyly, have been noted not infrequently. Bronsky, Kushner, Dubin and Snapper[3] have presented an excellent review of this subject.

In 1952, Albright, Forbes and Henneman[2] reported on a short, stocky patient with a typical round face, exhibiting brachydactylia, no intracranial calcifications but with soft tissue ossifications, irregular menses, no tetany, no abnormalities of serum calcium and inorganic phosphorus, and with no increased phosphaturic response to the Ellsworth-Howard test. Six cases of this syndrome of pseudo-pseudohypoparathyroidism had been reported (McNeely, Raisz and LeMay[7], Miles and Elrick[8], Roche[10], Seringe and Tomkiewicz[11], Wallach, Englert and Brown[15]) prior to 1959 when van der Werff ten Bosch[14] described 8 additional cases assuming that all patients with reduced stature and shortened lateral metacarpals, who lacked symptoms or signs of tetany, should be included in this category. All of the other characteristics of Albright's original patient have been absent in one or more of the subsequently reported cases of this syndrome. Gonadal dysgenesis, like soft tissue ossifications and calcifications, may or may not be present. Two of the 8 patients reported by van der Werff ten Bosch were brother and sister, while the occurrence in 2 sisters is noted in the report of Seringe and Tomkiewicz[11].

Case Reports. Three members of a family, the mother, son, and one daughter afflicted with this unusual malady, are reported. The remaining members of the family, the father and another daughter, are clinically normal. Only 2 of the patients would allow the Ellsworth-Howard test to be performed, and these insisted on receiving the hormone intramuscularly.

Case 1. E.E.K., a nurse's aid, 33 years old, was examined for nodules of the inner right forearm, present for 4 years, and of the outer mid-right thigh present for several months, both having been associated with increasingly severe burning pain.

At the age of 10 months, the patient had weighed 40 pounds. The right fourth toe had been very short since infancy, and at 23 years of age had become "infected and gangrenous," requiring amputation. At about the same time, the right hip had become stiff, sore and weak, and this had continued intermittently up to the present. An attack of meningitis in 1947 was followed by infrequent menses (about once every 8 months) and a scanty flow. Several respiratory infec-

tions had necessitated hospitalization during the past few years. She had been on thyroid extract for over a year for clinically diagnosed hypothyroidism. There had been no convulsions nor visual symptoms.

In 1951, a painful mass of "bony spicules and plaques measuring as much as half a centimeter in length" were removed from the dorsum of the left foot. No polyuria nor polydipsia had been noted.

The physical appearance of the patient was strikingly like that illustrated in Albright's classic article published in 1942. She was only 4 feet 11 inches in height, weighed 152 pounds, had a span between outstretched fingertips of 58 inches, and measured 29½ inches from tip of head to pubic symphysis, and 29½ inches from pubic symphysis to sole of foot. She had short, stubby fingers and short metacarpals with a wide palm, and short metatarsals, the right fourth toe being absent and the fourth metatarsal very short. The right hip revealed complete loss of internal rotation, a slight flexion contracture, and about 20% limitation of all other hip motions. All other joint motion ranges were normal, and motor power, reflexes, sensation, and cranial nerves were normal to examination. There were no circulatory changes nor neurological abnormalities. Mentality and personality seemed quite normal. There were no sexual nor other abnormalities on physical examination. Chvostek and Trousseau signs were negative. Ophthalmoscopic examination revealed no retinal changes, and no corneal, lenticular, or vitreous opacities. The nodules on the forearm and thigh were removed surgically on November 6, 1956, and found to consist of small well-differentiated bony plaques lying free in the fatty subcutaneous tissue just above the deep fascia, the bony trabeculae forming cystic spaces, and in some areas containing fibrillary yellowish-brown material.

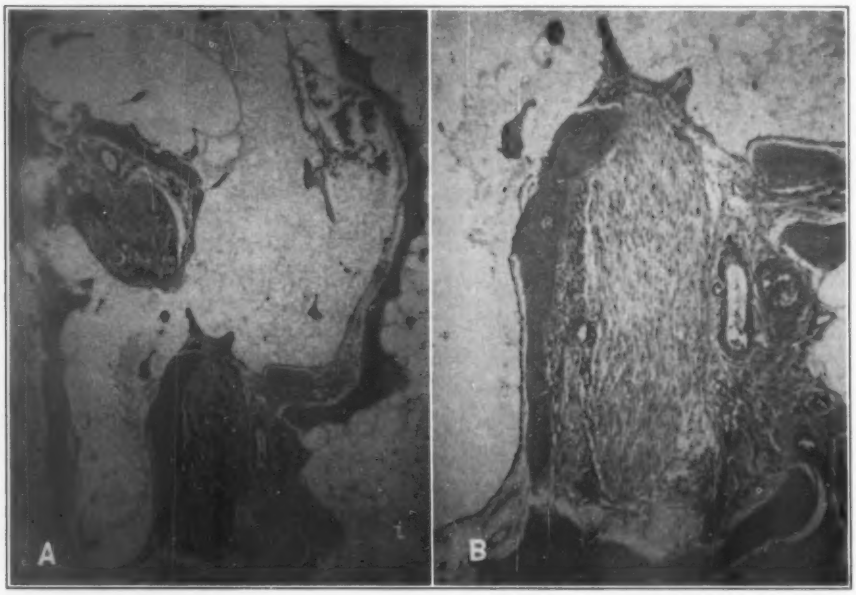

Fig. 1*A* and 1*B*.—Microscopic sections of subcutaneous bony nodule of patient E.E.K..

Roentgenograms revealed dysplasia of both hips, more marked on the right, and subcutaneous ossifications in the scalp, neck, forearms, thighs, legs, and feet, and exostoses of the tibiae. Dental films revealed no blunting of roots, or thickening of the lamina dura.

The administration of ACTH caused a drop in circulating eosinophils from 103 to 54 per c.mm. at 4 hours. The 24-hour urinary excretion of 17-ketosteroids was only 2.7 mg. in 24 hr. (normal 5 to 15 mg. in 24 hr.). The protein bound iodine (PBI) value was 4.7 μg. per 100 ml. Following a 10 microcurie dose of I_{131}, the 24-hour pickup was only

14.5%. After two doses of thyroid stimulating hormone (TSH), a second 10 μc. dose resulted in an increase in uptake of 4.5%. Basal metabolic rate readings were −22, −18, and −24%. Serum cholesterol was 320 mg. per 100 ml., the serum calcium, 10.2 mg. per 100 ml., the phosphorus 3.34 mg. per 100 ml., and the alkaline phosphatase 0.38 Bodansky units. A 24 hr. urinary Sulkowitch test was normal. The electroencephalogram (EEG) was normal for the patient's age. Fasting blood sugars were 88 and 96 mg. per 100 ml. A glucose tolerance curve revealed an elevation to 140 mg. per 100 ml. and a return to the fasting level in 2 hours. The erythrocyte count was 4.92 million, the hemoglobin, 12.8 gm., and the leukocyte count 5,800 with a normal differential and mild hypochromia of the red blood cells. Two sedimentation rates were 12 and 21 mm. Urinalyses were negative on 8 examinations, except for a 1 plus albumin on one occasion and a trace of sugar on another. A vaginal smear taken on the 23rd day of the cycle showed a moderate estrogenic effect. The insulin tolerance test revealed a normal hypoglycemic response (fasting 82 mg. per 100 ml.; 30 minutes, 45 mg.; 60 minutes, 52 mg.; 90 minutes, 72 mg.; and 120 minutes, 82 mg. per 100 ml.). The follicle stimulating hormone (FSH) urinary excretion in 24 hours was negative for 5, for 50 and for 100 mouse units, indicating an absence of urinary gonadotropin. The modified Ellsworth-Howard test demonstrated urinary phosphate excretion of 25.8 mg., two hours before, 22.4 mg. one hour before, and 24.2 mg. at the time of injecting 200 mg. of parathyroid hormone intramuscularly, and 21.0, 26.2, and 24.3 mg., one, two and three hours later.

Fig. 2.—Dysplastic right hip of patient E.E.K.

CASE 2. K.K. was the 36-year-old brother of the first patient. He had weighed 30 pounds at 6 months of age. At 2 years of age a mass of bone "the size of a plum" had appeared in the left groin. Excision had been advised but not performed. The mass spon-

taneously disappeared at the age of 5 or 6. At 9 years, a bony mass was removed from the left sole resulting in a stiff third left toe. No subsequent masses had developed, and he had never had any convulsions, eye symptoms or evidence of mental retardation. The history was entirely unremarkable except for a successful left inguinal herniorrhaphy performed in 1942.

The physical appearance was as striking as that of his sister. The head was rather large in proportion to the body, and baldness and pubic and axillary hair were all normally developed. No nodules were palpable. There had never been any polyuria or polydipsia.

Roentgenograms revealed ossifications in the basal ganglia (by laminography), malformed terminal phalanges of the big toes, and shortening of the fifth metacarpals and metatarsals. There was no blunting of the roots of the teeth. Small osteomata were present in the right fifth metacarpal, in the proximal phalanx of right ring finger, and in the left fifth metacarpal, the right humerus, and

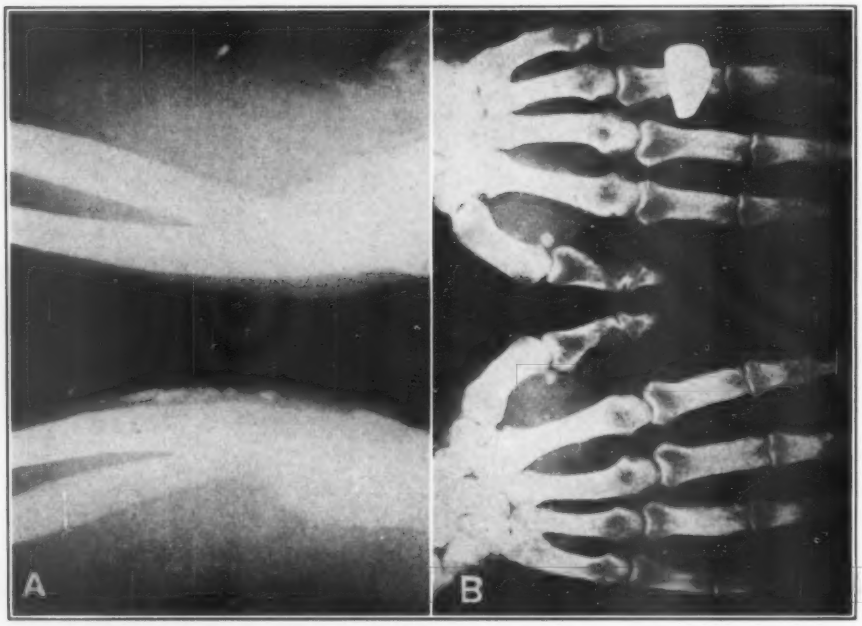

Fig. 3*A* and 3*B*.—Subcutaneous bony deposits on the forearms, and short metacarpals, in patient K.K.

had been present for 6 or 7 years. He was 4 ft., 11 in. in height, 174 pounds in weight, and the span between outstretched fingertips was 57 inches. He measured 29 inches from the tip of the head to the symphysis pubis and 30 inches from symphysis pubis to the soles. The hands and feet were abnormally short, especially the metacarpals and metatarsals. Intelligence was normal. There were no abnormalities of joint range, motor power, sensation, reflexes, cranial nerves, or circulation. The sexual characteristics were normal and the Chvostek and Trousseau signs were negative. There were no corneal, lenticular, or vitreous opacities. The testes, prostate, penis, the left radius. Both hips revealed mildly dysplastic acetabulae. There were many widely distributed subcutaneous ossifications of the scalp, neck, arms, forearms, hands, thighs, legs and feet.

The administration of ACTH caused a drop in circulating eosinophils from 156 to 59 per c.mm. The 24-hour urinary excretion of 17-ketosteroids was only 3.8 mg. in 24 hr. (normal 10 to 20 mg. in 24 hr.). After 5 daily injections of 40 units of ACTH, the excretion increased to 7.0 mg. The protein bound iodine (PBI) was only 1.1 μg. per 100 ml. The serum cholesterol was 380 mg. per 100 ml. The electroencephalogram revealed a slow

record for his age with some random 6 per second scattered dysrhythmia in all leads. The fasting blood sugar was 86 mg. per 100 ml. The glucose tolerance curve reached a peak of 148 and returned to normal in 2 hours. The erythrocyte count was 4.8 million, the hemoglobin, 13.7 gm., the leukocyte count 6,200, and the differential count was normal. The sedimentation rate was 8 mm. The semen volume was 5.5 ml.; the consistency watery, the count 61,100,000 per ml.; the total count being 336,050,000. The semen motility in 5 hours was 50%, 4 plus; 8 hours 25%, 3 plus, 24 hours 0. The morphology was normal: oval, 76%, abnormal; tapering 21%, round 2%, pinheads 1%. Conclusion: good fertility index. Urine analysis showed a specific gravity of 1.021, straw color, albumin negative, sugar negative. The microscopic examination of the urine showed few crystals. The serum calcium was 9.8 mg. per 100 ml., serum phosphorus 3.8 mg. per 100 ml., alkaline phosphatase 0.32 Bodansky units. The 24-hour urinary Sulkowitch test was normal. A modified Ellsworth-Howard test demonstrated urinary phosphate excretion of 26.4 mg., two hours before; 25.0 mg. one hour before; and 20.8 mg. at the time of injecting 200 mg. of parathyroid extract intramuscularly and 19.9 mg., 21.3 mg., and 21.4 mg., one, 2 and 3 hours later. A normal control on the same date had corresponding figures of 26.4 mg., 15.0 mg., 25 mg., and then 25.0 mg., 26.4 mg., and 26.4 mg. After the patient had been on a low calcium diet for several days, the serum calcium was 9.86 mg. per 100 ml., and the phosphorus 4.0 mg. per 100 ml. prior to the injection of 940 mg. of calcium as the gluconate-glucoheptinate intravenously during a 3½ hour period, and the levels were 10.84 and 3.4 respectively at the conclusion of this injection. Although the urinary excretion had been 133 mg. of calcium in the 24 hr. prior to the test, it was elevated to 180 mg. in the 24 hr. during and following the test (only accounting for 47 mg. of the 940 mg. of calcium injected).

CASE 3. E.K., the 57-year-old mother of these 2 patients was then examined. The past history included a stillbirth in 1927, followed by a hysterectomy in 1931. She had generalized "rheumatoid arthritis" which had necessitated almost complete bed rest for 3½ years. There had been no menstrual irregularities prior to the hysterectomy. Diabetes mellitus was diagnosed and treated with insulin from 1940 to 1944. She had never had any lumps, painful or otherwise, prior to 1952, when she noticed a painful burning and pressing pea-sized mass about an inch below the left mid-clavicle, followed a few months later by the development of similar small, slightly painful masses on both hands. Pain and swelling (but no "lumps") in the fingers, left shoulder, right elbow, right knee, and right great toe were also present, were considered recurrent rheumatoid arthritis, and subsided spontaneously. There were a few episodes of pain lateral to the left patella and over the anterior left ankle and the ball of the left foot. There had been no convulsions or visual difficulties.

The physical appearance was that of a wrinkled, much older person than 57 years, but she was quite intelligent and alert. She was 4 ft. 10¾ in. in height, weighed 130 pounds, and the span between her outstretched fingertips measured 59½ inches. The measurement from the tip of the head to the symphysis pubis was 28¾ inches, and from the latter to the soles was 30 inches. Her hands and feet were short but did not seem abnormally so. All joint ranges, motor power, reflexes, sensations, and cranial nerves were intact. The Chvostek and Trousseau signs were negative. There were no corneal, lenticular, or vitreous opacities. No subcutaneous nodules or masses were palpable.

Roentgenograms revealed only a few tiny ossifications in the subcutaneous tissues of the hand and feet, but no hip dysplasias or other malformations, and no brachydactyly.

The administration of ACTH caused a drop in circulating eosinophils from 212 to 37 per c.mm. The 24-hour urinary excretion of 17-ketosteroids was 3.4 mg. in 24 hours (normal adult female, 5 to 15 mg. per 24 hr.). The PBI was 4.4 μg. per 100 ml. The serum calcium was 9.3 mg. per 100 ml., phosphorus 3.5 mg. per 100 ml., and the alkaline phosphatase 6 King-Armstrong units. The urinary Sulkowitch test was normal. The electroencephalogram revealed a rather slow Alpha, probably normal low frequency record. The fasting blood sugar varied between 128 mg. and 356 mg. per 100 ml. The erythrocyte count was 3.72 million, the hemoglobin 10.3 gm. and there was slight hypochromia. The leukocyte count was 5,600 with a normal differential. The VDRL reaction, cephalin flocculation and the urinary Bence-Jones tests were negative. The hematocrit was 35% and the blood urea nitrogen, 14.2 mg. per 100 ml. The urinalysis showed a specific gravity of 1.029, no albumin, sugar 4 plus, acetone negative, an occasional red blood cell, 12 to 14 leukocytes per h.p.f., and rare casts. The electrophoretic plasma protein pattern was: total protein 5.7, albu-

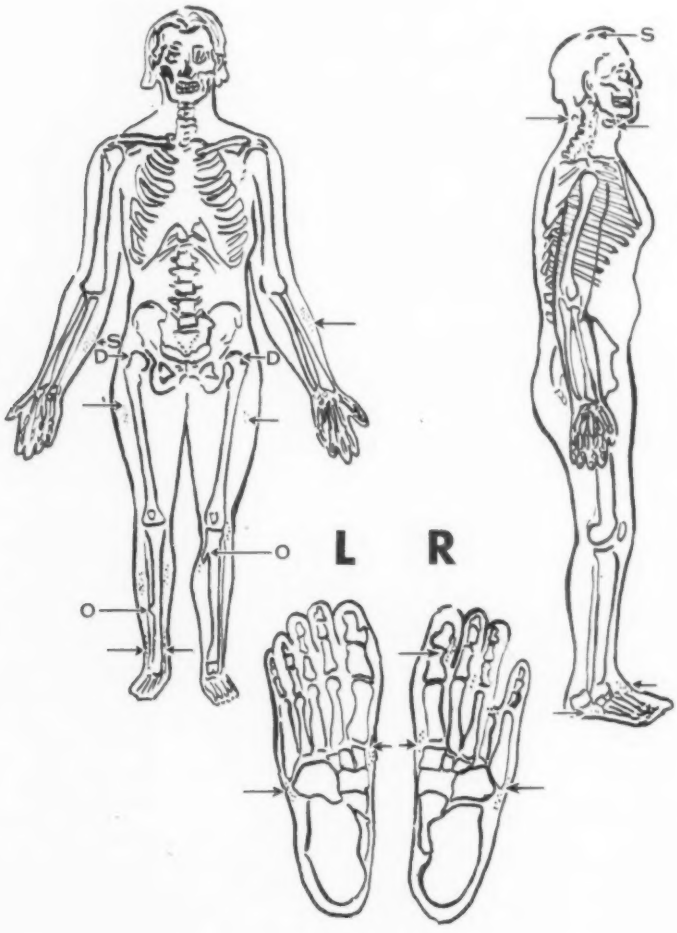

Fig. 4

min 50.3%, alpha 1, 3.6%; alpha 2, 14.6%, beta 14.6% and gamma globulin 16.8%, and an A/G ratio of 1.7 (revealing elevation of the alpha 2 fraction). The serum calcium was 10.0 mg. per 100 ml., the phosphorus 3.7 mg. per 100 ml. prior to the intravenous administration of 940 mg. of calcium as the gluconate-glucoheptinate during 3½ hours, and calcium 11.7 mg. per 100 ml., and phosphorus 3.1 mg. per 100 ml. at the end of this period. The urinary excretion of calcium had been 95 mg. in the 24 hours prior to the test, but was elevated to 244 mg. in the 24 hours during and after the test (accounting for 149 mg. of the 940 mg. of calcium injected). This patient refused to undergo an Ellsworth-Howard test.

SPECIAL STUDIES. In view of the known deposits of mucopolysaccharides in the subcutaneous tissues of myxedematous patients (Gabrilove and Ludwig[5]), and the probable relation of these substances to the initiation of ossification (Sobel and Burger[13]), special stains were used on tissues adjacent to bony deposits. No increase in mucopolysaccharides, however, could be demonstrated.

One patient's (the daughter's) serum was incubated with the epiphyseal

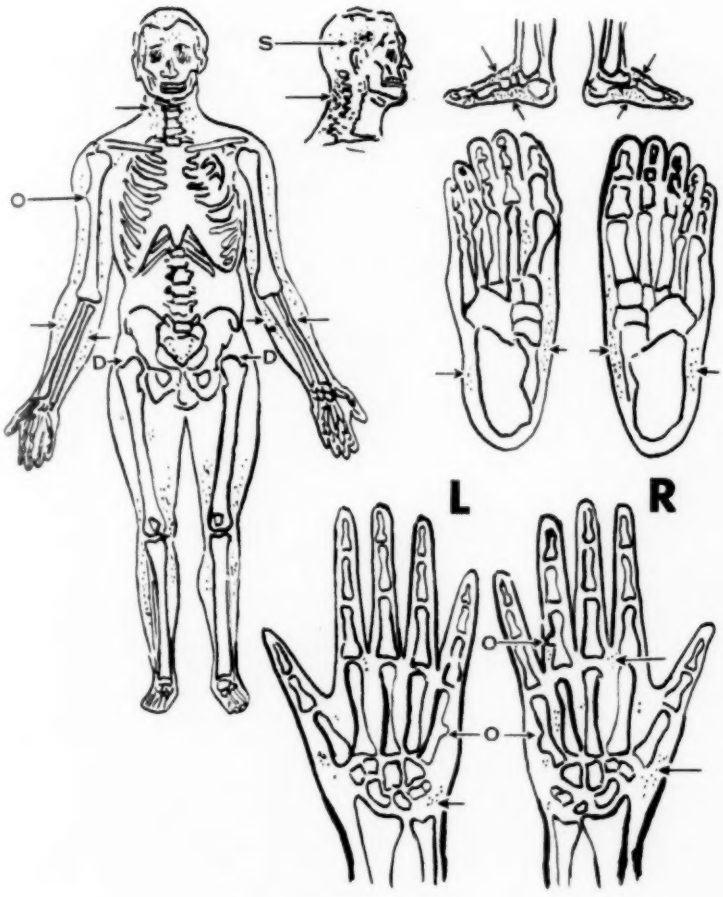

Fig. 5

cartilage of a rachitic rat, but calcification proceeded at the same rate as when the serum of a normal control was used (Sobel[12]). Tests were also made to determine the effects of the addition of either parathyroid hormone, magnesium sulfate, or beta glycerophosphate to the rachitic epiphysis immersed in one or other of the sera, but the calcification rate in the mixture with the patient's serum was still the same as that with the normal control serum and the corresponding mixture.

Discussion. Fromm[4] had expressed dissatisfaction with the term "Pseudo-pseudohypoparathyroidism" not only because of its paradoxical nature and its tongue-twisting features, but also because there is probably no relation of this syndrome to parathyroid function. There is a closer relationship to pseudohypoparathyroidism and to gonadal dysgenesis, and possibly even to myositis ossificans progressiva. The familial incidence, the dwarfism, and the brachydactyly suggest a developmental basis for the syndrome, with

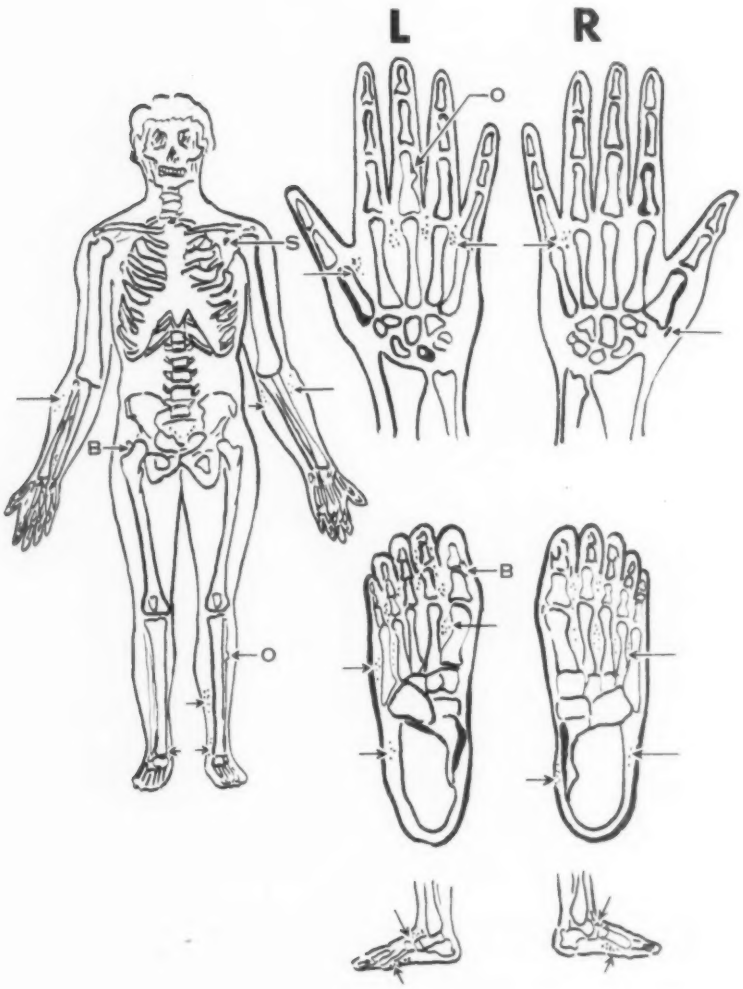

Fig. 6

Figs. 4, 5 and 6.—Distribution of bony nodules and deformities in patients E.E.K., K.K., and E.K. respectively.

O = osteoma

D = dyschondroplasia

S = subcutaneous bony deposits and deposits in basal ganglia in K.K.

B = accessory bone (ossicle)

subsequent changes after birth, such as spontaneously appearing, and occasionally receding, ossifications, as well as varying endocrine disturbances.

Summary. Three members of one family, a mother, daughter, and son were studied after the mother and daughter requested treatment for small painful subcutaneous nodules, and the diagnosis of pseudo-pseudohypoparathyroidism seemed probable.

These patients were stocky, under 5 feet in height, and had brachydactylia. Serum calcium, phosphorus and phosphatase determinations were normal. In 2 patients the Ellsworth-Howard test was performed, and although the parathyroid hormone had to be injected intramuscularly, no increased phosphaturia was noted. In addition to subcutaneous ossifications, there were such skeletal abnormalities as exostoses and hip dysplasias, and in one or more of the patients calcification of basal ganglia, diabetes mellitus, hypothyroidism, decreased urinary excretion of 17-ketosteroids, and absence of follicle stimulating hormone in the urine.

ACKNOWLEDGMENTS: I am deeply grateful to Dr. Gerd T. Schloss, pathologist, and to Drs. John A. Wilson and Andre J. Bruwer, roentgenologists, and their respective departments at Tucson Medical Center, as well as to the pathologists, Drs. Louis Hirsch and Ralph N. Fuller of Tucson, Arizona, for their generous and helpful suggestions.

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(Interlingua on page 497)

THE SPATIAL VECTORCARDIOGRAM AND VENTRICULAR GRADIENT IN APICAL MYOCARDIAL INFARCTION IN NECROPSIED PATIENTS*

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The spatial vectorcardiogram (sVCG) in apical myocardial infarction has received little attention. Although some investigators have attempted to construct QRS sÊ-loops from the electrocardiogram (EKG) (Burch and Winsor[7], Gardberg and Levy[9]), there are only a few published reports of the sVCG in this lesion (Grishman and Scherlis[10]). It was therefore considered of interest to study the records of patients with apical myocardial infarction established in the cardiovascular laboratories of the Tulane University School of Medicine and the Veterans Administration Hospital in New Orleans. This report concerns the results of that study.

Materials and Methods. The clinical and postmortem data of 12 patients in whom myocardial infarction resulted in scarring limited to the apex of the heart were available for study. In some of these patients the infarction extended toward the base; however, in every patient the apical region of the heart was primarily involved, and in most cases, completely scarred. Left ventricular hypertrophy was present in all except 2 patients (Table 1).

The patients ranged in age from 27 to 72 years with a mean of 59 years. All were males because of the nature of the hospital. Ten were white and 2 were Negro.

The spatial vectorcardiograms were recorded utilizing the tetrahedral reference system as previously described (Burch, Abildskov and Cronvich[3]). The conventional twelve-lead EKG was also recorded for each patient. Wire loop models of all the vectorcardiograms were constructed and studied (Fig. 1).

The ventricular gradient (Ĝ) was measured by methods similar to those described in previous reports from this laboratory (Burch and DePasquale[4,5,8]).

Results. ANATOMICAL CONSIDERATIONS. In 6 patients (Patients Number 1, 3, 5, 6, 8, 11) the infarct involved the apex of the heart alone (Table 1), and in 4 of these patients there was aneurysmal dilatation at the apex due to extensive scarring and loss of muscle. Of the remaining 6 patients, 2 had anterolateral and septal extensions (Patients Number 2, 12), one had anterior extension only (Patient Number 4), and 3 had posterior extension (Patients Number 7, 9, 10) of the infarct (Table 1). All but 2 patients had cardiac hypertrophy, and in every patient the left anterior descending coronary artery was markedly narrowed or occluded. In addition, the right posterior descending coronary artery was narrowed in one patient and occluded in another.

THE SPATIAL VECTORCARDIOGRAM. The results are summarized in Figs. 2 and 3 and Table 2.

*Supported by grants from the U.S. Public Health Service.

TABLE 1.—CLINICAL AND ANATOMICAL DATA FOR THE 12 PATIENTS WITH APICAL MYOCARDIAL INFARCTS

Patient Number	*Age*	*Sex*	*Race*	*Location of Infarct*	*Weight of heart gm.*
1	68	M	W	Apex	430
2	68	M	N	Apex with lateral and septal extension	365
3	65	M	W	Entire apex	567
4	27	M	W	Apex with anterior extension	429
5	40	M	W	Entire apex	481
6	58	M	W	Apex	200
7	69	M	W	Apex with posterior extension	405
8	65	M	N	Entire apex	452
9	66	M	W	Apex with posterior extension	610
10	72	M	W	Apex with posterolateral extension	630
11	65	M	W	Apex	324
12	44	M	W	Apex with lateral and septal extension	455

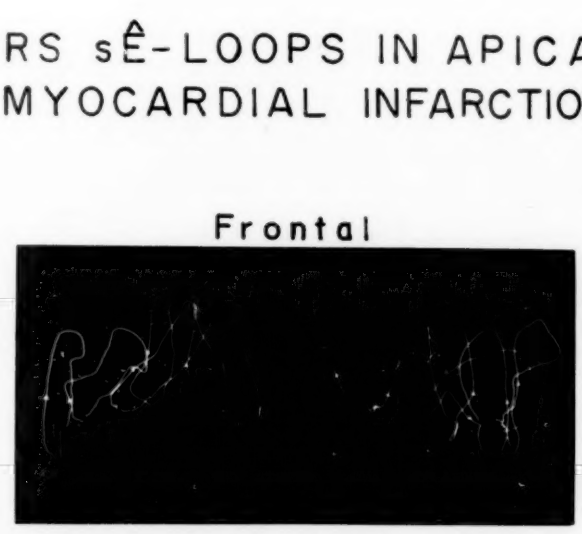

Fig. 1.—Constructed wire loop models for the 12 patients with apical myocardial infarcts. Note that most of the loops are oriented vertically toward −90°.

The QRS sÊ-loop was oriented to the left, superiorly and posteriorly, in all of the patients with apical myocardial infarction (Fig. 2 and Table 2). Six loops were inscribed in a clockwise direction and 6 in a counterclockwise direction. All except one were markedly distorted and narrow (Figs. 1, 3). Eight of the loops had a figure-of-eight configuration in either the frontal or left sagittal plane projection (Fig. 3). All but 2 of the loops were in the second sextant in the frontal plane projection (Fig. 2). The tendency for the QRS sÊ-loop to be oriented vertically in the frontal plane was the most remarkable feature of the vectorcardiograms.

TABLE 2.—MAXIMAL INSTANTANEOUS QRS sÊ-VECTORS IN THE 12 PATIENTS WITH APICAL MYOCARDIAL INFARCTION

	Maximal Instantaneous QRS Vector			
	Frontal Plane Projection		*Left Sagittal Plane Projection*	
Patient Number	*Direction degrees*	*Magnitude μv.s.*	*Direction degrees*	*Magnitude μv.s.*
1	— 77	2.05	−52	2.37
2	— 68	2.13	−63	2.37
3	— 88	2.45	−59	3.16
4	— 74	1.44	−65	1.54
5	−111	2.52	−57	2.52
6	— 82	2.73	−68	2.61
7	— 59	0.54	−93	0.68
8	— 28	0.70	−62	0.65
9	— 66	1.08	−54	0.85
10	— 68	2.14	−60	2.22
11	— 68	0.70	−62	0.70
12	— 90	1.13	−65	1.32
Mean	— 73	1.63	−63	1.74

MAXIMAL QRS VECTORS IN 12 PATIENTS WITH APICAL MYOCARDIAL INFARCTS

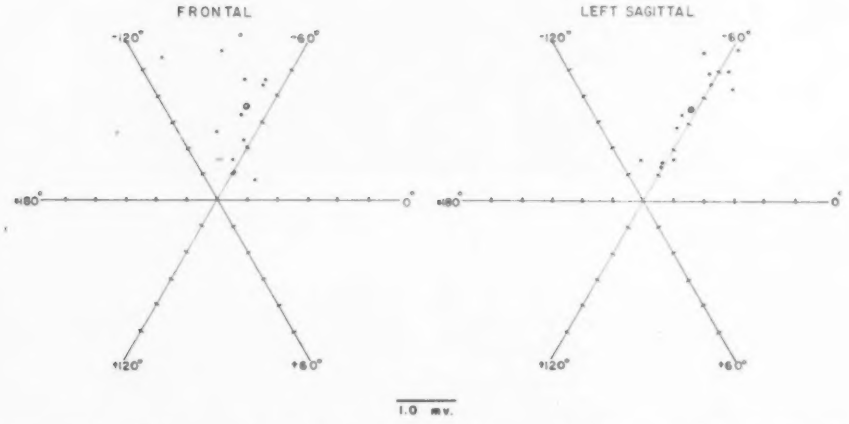

Fig. 2.—Spot graph of maximal QRS sÊ-vectors in the frontal and left sagittal plane projection. The mean is indicated by the open circle.

The T sÊ-loop was not inscribed in sufficient detail to be of diagnostic value in the 12 patients.

THE VENTRICULAR GRADIENT. The results are summarized in Figs. 4 and 5 and Table 3.

The $\hat{A}_{QRS}$ was oriented to the left and upward in the frontal plane, with only one vector oriented below the horizontal axis of the triaxial reference system (Fig. 4). The mean direction of $\hat{A}_{QRS}$ was 38° and the mean magnitude 30.6 μv.s. (Fig. 5). The $\hat{A}_T$ was directed downward in the frontal plane (Fig. 4) with a mean direction of 89° and mean magnitude of 25.0 μv.s. (Fig. 5). The ventricular gradient ($\hat{G}$) was oriented to the left in the frontal plane with a mean direction of 6° and was shorter than normal* with a mean magnitude of 27.6 μv.s. (Fig. 5).

The $\hat{A}_{QRS}$ was to the left of $\hat{G}$ in all but 2 patients, and the angle between $\hat{A}_{QRS}$ and $\hat{G}$ was greater than 35° in all but 3 patients (Table 3).

The ventricular gradient was abnormal in every instance due to position (6 patients), magnitude (2 patients), abnormally wide angle between $\hat{A}_{QRS}$ and $\hat{G}$ (9 patients), or to a combination of these factors (4 patients). Because the magnitude of $\hat{G}$ was decreased, the ratio of $\hat{G}$:$\hat{A}_{QRS}$ was less than unity in 9 patients.

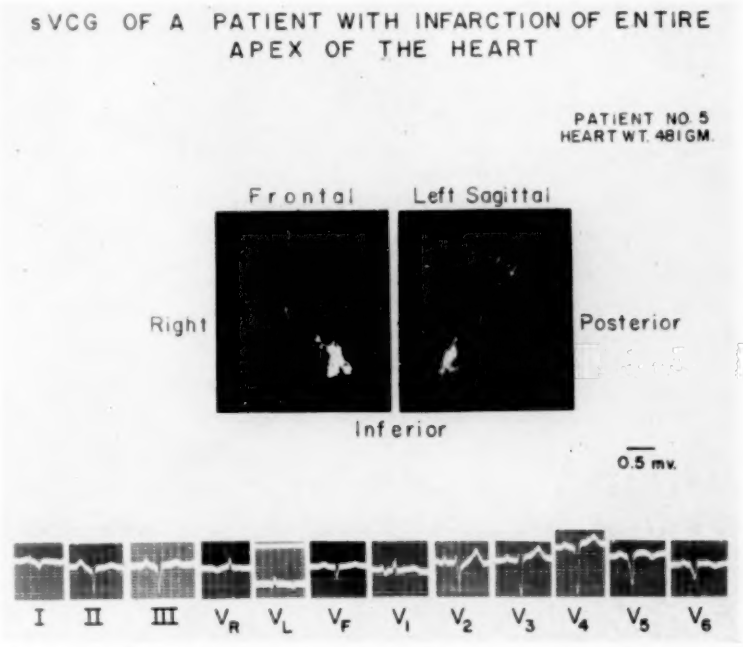

Fig. 3.—sVCG of a patient with infarction of the entire apex of the heart.

Discussion. Apical myocardial infarction was associated with considerable myocardial damage in the areas supplied by the anterior descending

*The normal values calculated from Ashman[1] for adult men and women using 2 standard deviations are, for G, +39.2° (2.2°–72.2°), 46.2 (13.5–78.9) μv.s. and, for A_{QRS}, +41.7° (−21.5° – +104.9°), 21.8 (3.1–40.6) μv.s.

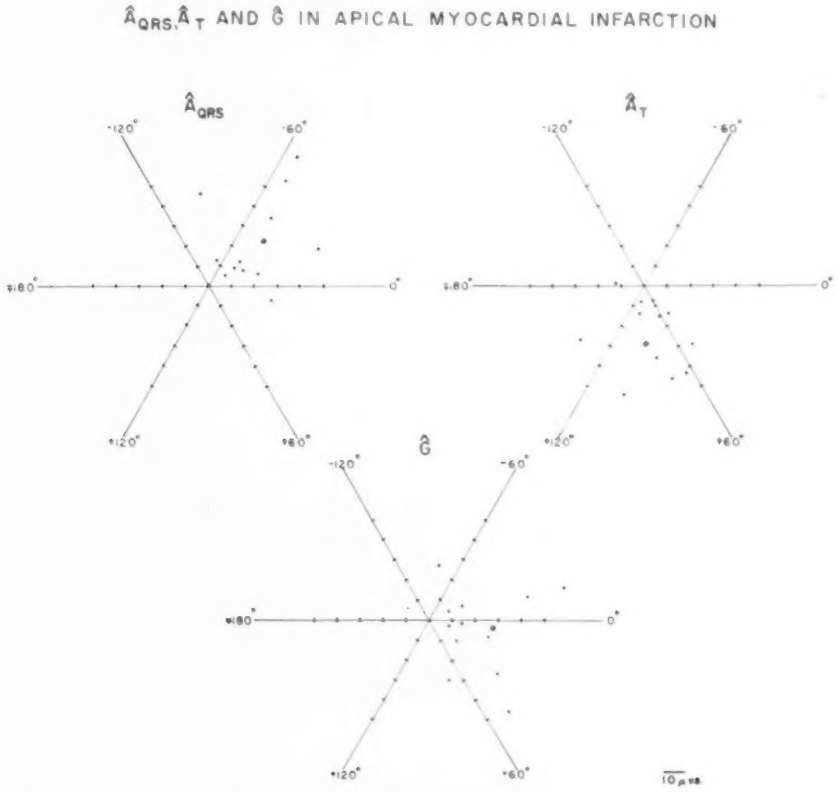

Fig. 4.—Spot graph of $\hat{A}_{QRS}$, $\hat{A}_T$ and $\hat{G}$ in the frontal plane. Means are indicated by the open circles.

TABLE 3.—THE DISTRIBUTION IN NUMBER OF PATIENTS OF THE MAGNITUDE OF THE ANGLE BETWEEN $\hat{A}_{QRS}$ AND $\hat{G}$

Position of $\hat{A}_{QRS}$ Relative to $\hat{G}$	*Number of Patients*	*0°–35°*	*36°–70°*	*>70°*
Right	2	2	–	–
Left	10	1	8	1

branch of the left coronary artery. When the posterior descending coronary artery was not extensively involved with atherosclerosis, as was the case in all except 2 of the patients in this series, then the effects of the electric forces from the basal portion of the left ventricle predominated. With extensive infarction of the apex of the heart, the initial forces of ventricular activation were directed to the right and posteriorly, producing Q waves in leads I and II of the electrocardiogram. In several instances anterolateral and diaphragmatic infarcts resulted in vectors which, during the first 0.04 second of ventricular activation, were also directed to the right, so that Q waves were displayed in lead I or in leads I and II. However, when the postero-

basal portion of the left ventricle was spared, as in the patients with relatively healthy right coronary arteries, the late vectors of ventricular activation helped in the diagnosis of apical myocardial infarction. The late vectors of ventricular activation progressing through the basal regions of the heart are expected to be directed to the left and posteriorly; and since the basal region was the healthiest portion of the heart, these late vectors were the pre-

All of the loops enclosed a small area such as those described previously from this laboratory for diffuse myocardial disease (Burch, Horan and Cronvich[6]). This narrow loop is a fairly reliable vectorcardiographic expression of widespread myocardial disease such as may be associated with apical infarction. The presence of aneurysmal dilatation of the apex in 4 of the 12 patients is further evidence of such widespread disease. It should be pointed out that

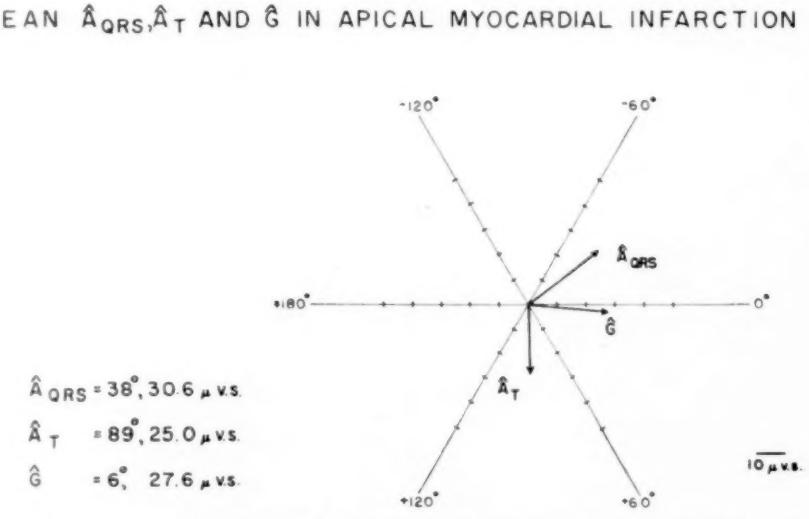

Fig. 5.—Mean $\hat{A}_{QRS}$, $\hat{A}_T$ and $\hat{G}$ for the 12 patients with atypical myocardial infarcts.

dominant cardiac electric vectors. It seems, therefore, that the QRS sÊ-loop should be uniformly directed superiorly. Of the 12 patients described in this report, all but two had QRS sÊ-loops which were oriented posteriorly in the left sagittal plane projection. The rotation of the loops was not consistent. Eight of the loops had a figure-of-eight configuration in either the frontal or left sagittal plane projections. This feature of the QRS sÊ-loop in apical infarction has been noted by other authors (Gardberg and Levy[9]).

all but 2 of the patients had left ventricular hypertrophy (LVH) which alone tends to produce a wide elliptically shaped QRS sÊ-loop. However, only one patient had this type of QRS sÊ-loop, which is still further evidence of the widespread myocardial disease associated with apical infarction of the heart.

The ventricular gradient was abnormal in all 12 patients. In 6 patients it was deviated abnormally to the left. In 2 patients the magnitude of $\hat{G}$ was less than normal. The angle between

$\hat{A}_{QRS}$ and $\hat{G}$ was greater than 35° for 9 patients. The mean magnitude of this angle was 45°, the range being 14° to 116°. In a previous study of 172 electrocardiograms, it was found that the angle between $\hat{A}_{QRS}$ and $\hat{G}$ was greater than 35° in only 3 subjects (Burch and DePasquale[4]). The deviation of $\hat{A}_{QRS}$ to the left without a commensurate shift in $\hat{A}_T$ resulted in a $\hat{G}$ that had a mean magnitude less than normal for the 12 patients. This is best expressed by the $\hat{G}:\hat{A}_{QRS}$ ratio which was less than unity in 9 patients. The normal value for this ratio is usually between 2 and 3 (Ashman and Byer[2]).

Summary. The spatial vectorcardiogram and ventricular gradient were studied in 12 patients with apical myocardial infarction established at necropsy. The QRS sÊ-loops were uniform in configuration with one exception (Patient Number 8). They were oriented vertically in the frontal plane projection and were narrow and distorted.

The ventricular gradient was abnormal in all of the patients; in 6 because of position, in 2 because of magnitude, in 9 because of its abnormal angular relationship to $\hat{A}_{QRS}$, and in 4 because of a combination of these factors.

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SUMMARIO IN INTERLINGUA

Le Vectocardiogramma Spatial e le Gradiente Ventricular in Infarcimento Myocardial Apical, Studiate in Casos Venite al Necropsia

Le vectocardiogrammas e le gradientes ventricular esseva studiate in 12 patientes in qui infarcimento myocardial apical esseva establite al necropsia. Le ansas sÊ de QRS esseva uniforme in lor configuration, con un exception (patiente 8). Illos esseva orientate verticalmente in le projection del plano frontal. Illos esseva distorquite e reducite in lor largor.

Le gradiente ventricular esseva anormal in omne le patientes: In 6 in position, in 2 in magnitude, in 9 in le relation angular a $\hat{A}_{QRS}$, e in 4 in un combination de iste factores.

ARTERIAL PULSE RECORDING IN PERIPHERAL VASCULAR DISEASE

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When the instrumental evaluation of peripheral arterial disorders is considered, it is important to distinguish between the examination of the arterial part of the circulation, integrated by medium-sized muscular arteries, such as the femoral, brachial or popliteal, and the arteriolar and capillary portion, which constitutes the terminal part of the circulation (Goetz[7]). For the study of the latter, the more adequate methods are digital plethysmography (Buzzi[3]) and the measurement of skin temperature (Buzzi[2]), and they will not be discussed here.

Currently, the pulsatility of the arteries of the extremities is investigated, if we exclude manual palpation, almost exclusively by oscillometry. This procedure has been extensively used during the last three decades for study of peripheral arterial patients. Although its introduction in clinical practice has constituted a significant advance, certain limitations of the procedure should be mentioned (Buzzi[1,4]): 1) Graphic recording is available in a limited number of instruments. Even when feasible, it is performed with mechanical methods, with considerable inertia. Paper speed is slow, and certain morphologic changes of the arterial pulse curve are poorly discernible in these tracings. 2) The sensitivity is usually low, and occasionally palpable arterial pulses are not recorded by the oscillometer. 3) Its calibration is arbitrary, and not the same in different machines. Its results can be modified by changing the position of the pneumatic cuff, and they are not comparable, therefore, in different patients, and not even in the same subject at successive examinations. 4) The nature of the pneumatic cuff poses by itself a problem, as it includes two arteries in certain territories, such as the forearm and leg, making it impossible to ascertain the degree of occlusion of a single vessel. 5) Certain vascular regions, such as the palmar, plantar and digital arteries are difficult to explore with this instrument.

The introduction of accurate manometers, with a wide range of sensitivity, and electronic recording methods, permit the obtaining of arterial pulses at different levels of the vascular tree, either by direct or indirect methods.

It is the purpose of this paper to present a study of peripheral arterial pulses in patients with vascular obstruction, discussing at the same time the clinical value of the procedure.

Material and Methods. Arterial pulses were obtained by puncture of both femoral arteries in 3 patients with aortoiliac thrombosis, and of both radial arteries in one patient with a subclavian arterial obstruction of atherosclerotic origin. Cournand needles, 18 gauge, were employed for puncture performed at the inguinal regions and at the wrist, respectively. These parts were previously anesthetized with 1% procaine. The needles were connected, by means of plastic tubing, to Statham P23A manometers, which were calibrated in order to assure an equal sensitivity and baseline in both. By means of adequate supports, an identical level was used. Amplifying and recording were made by means of a 4-channel oscilloscope. The electrocardiogram (lead II) was simultaneously obtained. Mean pressures were electronically integrated. Recording was made at paper speed of 25 and 75 mm. per second.

Indirect recording of the peripheral arterial pulses was performed in 20 patients with atherosclerosis obliterans of the lower limbs. A total of 35 tracings was obtained in this group of patients. Another 37 tracings were recorded in a group of normal subjects and hypertensive patients without arterial stenosis or occlusion. A capacitative manometer was employed. It consists of a small metal capsule, 5.5 cm. long and 2.7 cm. wide. One of its faces is covered with a rubber membrane. This surface is applied to the skin overlying the vessel to be investigated. Adequate contact is secured by means of a rubber band. The pressure employed should be slight. Repeated trials using different pressures may be sometimes necessary. The mechanical displacement is transformed into electrical impulses which are amplified and recorded by a direct writing electrocardiograph at a paper speed of 25 mm. per second. In this study the manometer was placed over the popliteal, dorsalis pedis, posterior tibial, plantar, palmar and digital arteries. Morphologic analysis included peak sharpness, presence of dicrotic wave and incisura. The crest time was also determined. Comparison of the tracings obtained over the radial and dorsalis pedis arteries was made.

Results. a) DIRECT ARTERIAL PULSE RECORDING. *Case 1.* A 59-year-old man, complained of intermittent claudication of 6 months' duration, localized at the right hip and thigh. He had had a cerebral thrombosis with hemiplegia one year previously. He had also noted effort and paroxysmal nocturnal dyspnea during the last 3 months. Physical examination revealed a diminished right femoral pulse, and absence of both posterior tibial and dorsalis pedis pulses. The right brachial arterial pressure, was 140/80 mm. Hg. Cardiac enlargement and moist basal pulmonary rales were present. Direct pressure curves from both femoral arteries showed reduced systolic and mean pressures on the right side. The diastolic pressure, however, was more elevated at the right femoral artery, as can be seen in the tracing obtained at a speed of 75 mm. per second (Fig. 1). The blood pressure at the right femoral artery was: systolic 83, diastolic 60, mean 68 mm. Hg. The mean systolic pressure was 75, mean diastolic pressure 62 mm. Hg. In the left femoral artery, the systolic pressure was 120, diastolic 50, mean 74 mm. Hg. The mean systolic pressure was 91.5, mean diastolic pressure 58 mm. Hg. The systolic gradient was 37 and diastolic 10, the mean gradient 6 mm. Hg. The mean systolic gradient was 16.5 and the mean diastolic gradient 4 mm. Hg (Fig. 2).

Case 2. A 53-year-old man, complained of bilateral intermittent claudication, more marked on the right side, of 1 year's duration. Physical examination revealed diminished femoral pulses, especially the right, and absence of popliteal, posterior tibial, and dorsalis pedis arterial pulses. Direct femoral curves indicated reduction of pulse pressure, and rounding of the systolic peak. The lower curve is delayed in comparison with the upper tracing. Left femoral arterial pressure was systolic 118, diastolic 104, mean 112 mm. Hg. The right femoral arterial pressure was systolic 70, diastolic 62, mean 64 mm. Hg (Fig. 3).

Case 3. A 46-year-old man, complained of intermittent claudication localized at the right thigh, but occasionally referred to the calf, of 14 months' duration. He had noted Raynaud's phenomenon in the right index and left ring fingers on exposure to cold. Physical examination revealed marked reduction of the amplitude of the right femoral pulse, and absence of the other pulses of the right lower limb. In the left leg, all arterial pulses were present. Femoral intraarterial pressures indicated a normal left femoral pulse, and a reduction of systolic and diastolic pressures on the right side. The left femoral arterial pressure was systolic 156, diastolic 84 mm. Hg. The right femoral pressure was systolic 80, diastolic 66 mm. Hg (Fig. 4).

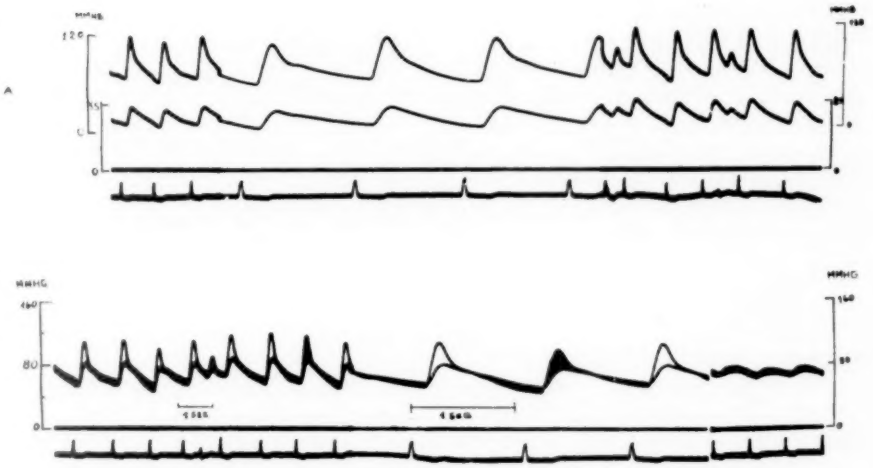

Fig. 1.—Simultaneous curves from the left femoral artery, right femoral artery, and electrocardiogram (lead II) of case 1. The upper curve is normal, the lower tracing shows diminished systolic and mean pressures. *B*: Same curves with superimposed baselines for the calculation of systolic and mean gradients. Paper speed: 25 and 75 mm. per second.

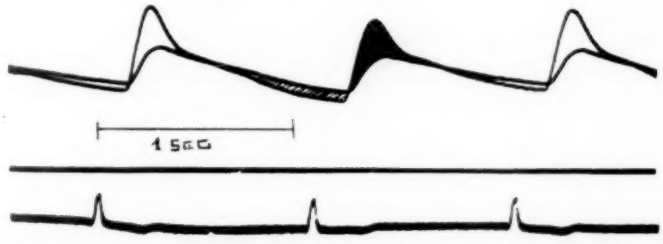

Fig. 2.—Enlargement from Fig. 1, showing details of systolic and diastolic gradients.

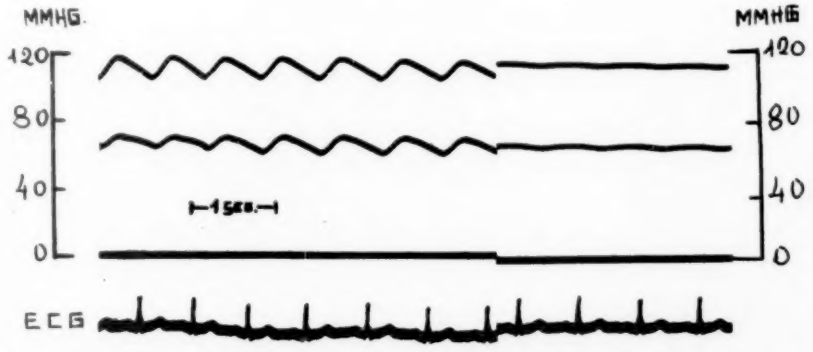

Fig. 3.—Femoral pulses from case 2. Both are abnormal, and show reduced pressure values, and rounded peak (see text).

Case 4. A 47-year-old man, complained of intermittent claudication localized in both calves, and the left arm and forearm, of one year's duration. Physical examination revealed bilateral absence of popliteal, dorsalis pedis and posterior tibial pulses. The axillary, brachial, radial and cubital were impalpable at the left upper limb. Pressure tracings obtained from both radial arteries at the wrist, showed a popliteal artery, and at the aortic bifurcation. The occurrence of distal lesions involving small vessels is infrequent, except in diabetics, and in patients over 60 years of age. When an occlusion at the middle or lower third of the femoral artery is suspected, placement of the sensitive capsule at the inguinal region over the femoral artery, and at the popliteal fossa, permits localization and evaluation of the

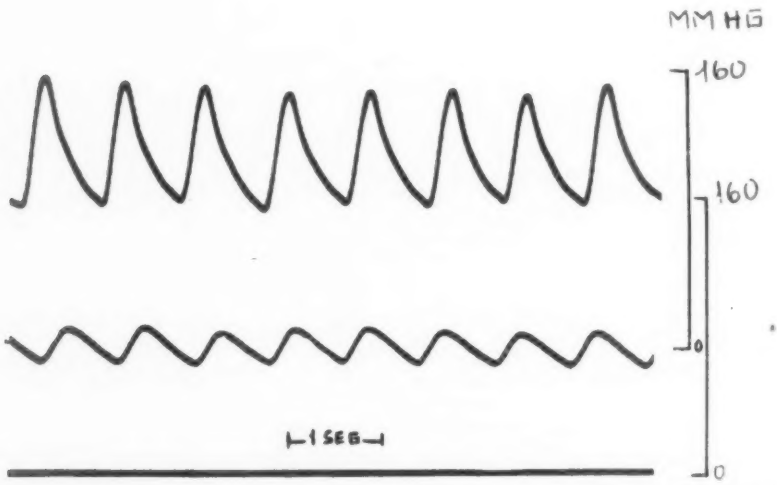

Fig. 4.—Pressure curves successively (and not simultaneously) obtained at the left (upper curve) and right (lower curve) femoral arteries (case 3). The left femoral arterial pulse is normal, while the right femoral shows the morphologic and quantitative characteristics of the poststenotic arterial pressure curve.

normal contour at the right side, while in the left, reduced values were present for the systolic, diastolic and mean pressures. The lower curve was definitely delayed in comparison with the upper tracing. Right radial arterial pressure was systolic 140, diastolic 100, mean 120 mm. Hg. Left radial pressure was systolic 88, diastolic 82, mean 86 mm. Hg.

b) INDIRECT ARTERIAL PULSE RECORDING. Peripheral atherosclerosis is more frequently localized at the lower third of the superficial femoral artery, the severity of the lesion. In either aortic or iliac occlusion, recording of the brachial and femoral or popliteal pulses allows, similarly, the evaluation of the severity of the obstruction and the extent of collateral circulation.

Investigating the pulsatility of the dorsalis pedis and posterior tibial arteries, when these vessels were impalpable, we have been surprised with the frequency with which the electronic sphygmograph reveals satisfactory pulsations, when the oscillometric index was zero. This finding is particularly

significant when arterial graft surgery is considered. In effect, the feasibility of placing an arterial plastic prothesis depends, apart from the length of the occlusion of the main arterial trunk, on the patency of the distal circulation. Angiography has been almost the only procedure employed for this purpose, but occasionally the plantar and digital arteries are not visualized, even when patent. The recording of an arterial pulse curve of adequate amplitude assures the patency of the distal circulation, with the advantage of being a simpler and safer procedure than angiography.

Palpation of the popliteal artery can be, under certain circumstances, as in obesity, difficult to perform. When the superficial femoral artery is occluded, the patency of the popliteal artery assures the blood flow to the leg and foot, while its obstruction is of serious prognostic significance. In these cases, oscillometry can furnish equivocal results, while a tracing with a pulse curve of satisfactory amplitude indicates the patency of the vessel. The modifications of the arterial pulse curve produced by vascular obstruction can be of different degree. When arterial stenosis is moderate, the curve's amplitude is diminished, and the peak is rounded and delayed, and dicrotic phenomena are absent. When the obstruction is severe, and collateral circulation inadequate, the curve is flat, and markedly reduced in amplitude. Its peak may be poorly discernible. The failure to obtain pulsatile phenomena over the course of the arteries currently explored, such as the popliteal, dorsalis pedis, or posterior tibial, or over the plantar arteries, is in our experience of bad prognostic significance, as far as limb survival is concerned.

The measurement of the time between the beginning of the anacrotic limb, and the systolic peak (crest time), is a quantitative index, that has clinical value for the constancy with which it is altered in arterial stenosis or occlusion. It is particularly useful when the pulse amplitude is not markedly reduced, as can happen when the arterial lesion involves up to 60% of the vascular lumen. We have determined crest time in 72 indirect pulse tracings. Extreme values were 0.10 and 0.40 second, with an average of 0.118 second for the normal subjects, and 0.213 second for the patients with arterial obstruction. In the normal patient, the crest time varies between 0.10 and 0.14 second, but if marked vasodilation is present, it can be shorter. In atherosclerotic patients it varied between 0.18 and 0.40 second. Values between 0.14 and 0.18 second are of difficult interpretation. In our series we have six tracings with crest times around 0.16 second. Three of them belong to patients with arterial obstructive lesions, and the other 3 to subjects without arterial occlusion. One of this last group had arterial hypertension, and the other two were over 60 years of age. Values from 0.14 to 0.18 second could represent, therefore, initial or asymptomatic arterial lesions (Fig. 5 and 6).

During the clinical examination of peripheral vascular patients, the digital, palmar and plantar arteries are seldom explored. A knowledge of the state of these vessels is, however, of considerable clinical importance. In patients with digital arterial syncope, it is necessary to distinguish between a purely functional state, and organic lesions of the arteries. Although some clinical manifestations, such as its asymmetry, persistence, and evidence of organic arterial disease elsewhere suggest an organic basis, the final diagnostic evidence will be obtained through the recording of an arterial pulse curve

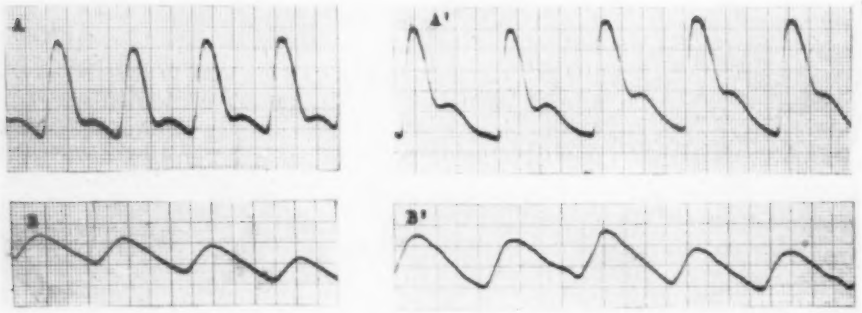

Fig. 5.—*A* and *A'*: Indirectly obtained pulses from the dorsalis pedis arteries of 2 normal subjects. *B* and *B'*: Dorsalis pedis pulses from two patients with atherosclerotic obliteration of the superfitial femoral artery. The curve's amplitude is diminished, its peak is rounded and delayed, and dicrotic phenomena are absent.

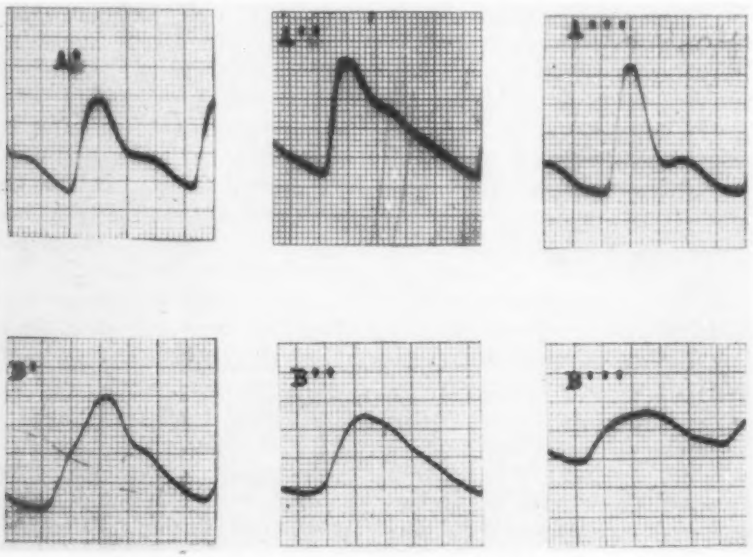

Fig. 6.—*A'*, *A"* and *A"'*: Pulses indirectly obtained from the popliteal, posterior tibial, and dorsalis pedis arteries of normal subjects. *B'*, *B"* and *B"'*, pulses from patients with obliterative arterial disease (see text).

which will be normal in amplitude and morphology between the attacks in true Raynaud's disease, without organic changes of the digital arteries (Fig. 7).

The recording of the arterial pulse curve with equipment of high sensitivity permits the detection of pulsatile phenomena, which ordinary methods are incapable of recognizing (Samuels[11]). When the dorsalis pedis and posterior tibial pulses are impalpable, and even the oscillometric index is zero, but satisfactory pulsation can be recorded in these vessels, as well as over the plantar arteries with an electronic manometer, it can be presumed

that an adequate peripheral blood flow is present under basal conditions in spite of arterial occlusion. The repeated finding of complete absence of pulsatile phenomena, on the other hand, indicates a severe deficiency of the distal circulation.

Discussion. It has been experimentally shown (Haimovici[8]) that a reduction of 60% of the aortic diameter does not produce significant changes of arterial blood pressure, while a value, however, an important reduction of arterial pressure was observed. Other studies have shown (Wylie and McGuinness[12]) that the arterial lumen needs to be reduced 90% in order that ischemic symptoms be present.

These experimental studies indicate that when clinical manifestations appear, arterial disease is already advanced from a pathologic point of view, the vascular stenosis is marked, and a complete occlusion is usually present.

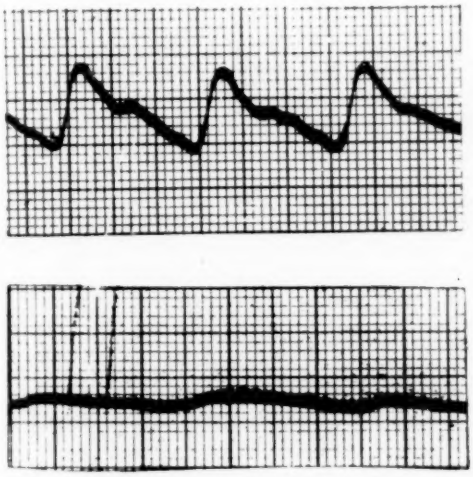

Fig. 7.—Upper curve: Pulse of a digital artery from a normal subject. Lower curve: Digital artery's pulse from a patient with Raynaud's phenomenon and organic changes of the digital vessels (see text).

diminution of between 60 and 70% results in definite manometric changes. When the diameter is reduced to 70%, a critical point is reached, beyond which an additional reduction produces a marked lowering of the mean arterial pressure. In an investigation (Haimovici and Escher[9]) in which the reduction of the aortic lumen cross section area, and not the aortic diameter, was studied, it was found that a diminution up to 82% of the cross section area did not produce significant hemodynamic changes. Beyond this In the initial period, however, the lesion is segmental and localized, and an arterial graft is, therefore, feasible.

The analysis of the direct arterial tracings from our patients shows that the characteristic signs produced by stenosis or occlusion of the aortic bifurcation are a rounding of the curve, a more oblique anacrotic limb, disappearance of dicrotic phenomena, and reduction of systolic and mean pressures. The fate of the diastolic pressure depends on the anatomic conditions distal to the point of measure-

ment. In effect, if the arterial circulation beyond the lesion is normal, the diastolic pressure will be reduced in proportion to the lowering of the systolic pressure. In those cases with additional distal arterial lesions, on the other hand, a relative increase of the diastolic pressure is present. This phenomenon can be interpreted as a result of the augmented peripheral resistance that these lesions can produce. When a quantitative estimate of an aortic or iliac obstruction, or both, is considered necessary, the calculation of systolic, diastolic and mean gradients is particularly useful. Recording with superimposed baselines greatly facilitates these calculations.

A direct estimation of intraarterial pressure beyond a stenotic lesion may not always be desirable or feasible. The puncture of some peripheral arteries, as the popliteal, is difficult to perform. When the arteries of the limbs are impalpable, moreover, its puncture is too cumbersome and impractical to be of current clinical value. In these conditions, the indirect recording of the arterial pulse, although lacking the accuracy of direct measurement, gives qualitative information of much clinical importance. The finding of pulsatile phenomena of satisfactory amplitude over the course of impalpable peripheral arteries indicates that an inadequate blood flow is not present during basal conditions. The delay of the systolic peak beyond 0.14 second, as well as its rounding, absence of dicrotic wave and incissura, diminished amplitude, and sinusoidal aspect of the curve, constitute additional evidence suggestive of occlusive arterial disease. The indirect procedure, moreover, permits the examination of arterial territories not commonly explored, such as the palmar and plantar circulations. In addition to its diagnostic significance, indirect arterial pulse recording offers particular prognostic value. In this respect, the repeated absence, after release of vasomotor tone with reflex vasodilatation or nitroglycerin administration, over the course of distal impalpable arteries, such as the dorsalis pedis, internal plantar, or posterior tibial, indicate a grave outlook. A tracing with a recognizable arterial curve, although rounded or flattened, and with a markedly delayed peak, on the other hand, suggests a more favorable clinical course.

Summary. The instrumental procedures which evaluate the pulsatile arterial circulation are analyzed. The importance of distinguishing the arterial part of the circulation, from the arteriolar and capillary portion, is emphasized.

The femoral intra-arterial tracings, simultaneously obtained with the electrocardiogram, of 3 patients with atherosclerotic stenosis of the aortic bifurcation, and of one patient with a left subclavian arterial obstruction of atherosclerotic origin, are presented. The morphologic changes of the arterial curve (slow ascending anacrotic limb, delayed systolic peak, and rounding of the pulse curve, as well as the pressure differences between both superimposed tracings (systolic, mean, and diastolic gradients) are analyzed.

Data on indirect pulse recording of arteries of the limbs (dorsalis pedis, posterior tibial, popliteal, plantar) from 20 patients with atherosclerosis obliterans of the lower limbs, are reported, with special reference to crest time. Mention of the clinical value of the indirect examination of the plantar and palmar circulations with electronic methods is made. The diagnostic and prognostic significance of direct and indirect pulse recording in peripheral arterial disease is discussed.

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SUMMARIO IN INTERLINGUA

Registration del Pulso Arterial in Morbo Periphero-Vascular

Es analysate le manovras instrumental que servi a evalutar le pulsante circulation arterial. Es sublineate le importantia de distinguer le parte arterial del circulation ab le parte arteriolar e capillar.

Le registrationes intra-arterial femoral, obtenite—simultaneemente con le electrocardiogramma—in 3 patientes con stenosis atherosclerotic del bifurcation aortic e in 1 patiente con un obstruction arterial sinostro-subclavian de origine atherosclerotic, es presentate. Le alterationes morphologic del curva arterial (lente ascension del branca anacrotic, retardo del culmine systolic, arrondage del curva de pulso) si ben como le differentias de pression inter le duo superimponite registrationes (gradientes systolic, medie, e diastolic) es analysate.

Datos relative al indirecte registration de pulso in le arterias del extremitates (dorso-pedal, postero-tibial, popliteal, plantar) ab 20 patientes con atherosclerosis obliterante del extremitate inferior es reportate con referentias special al tempore de cresta (intervallo inter le initio del branca anacrotic e le culmine systolic). Es mentionate le valor clinic del examine indirecte del circulationes plantar e palmar per medio de methodos electronic. Es discutite le signification diagnostic e prognostic de directe e indirecte registrationes de pulso in morbo periphero-arterial.

EVALUATION OF THE NITRITES IN THE TREATMENT OF ANGINA PECTORIS

ERYTHROL TETRANITRATE (ETN) AND PENTAERYTHRITOL TETRANITRATE (PETN) AS THERAPEUTIC AGENTS

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Since the first description of angina pectoris by Heberden[2] nearly 200 years ago, countless preparations have been introduced for the treatment of this disorder. None, however, have proved equal to the nitrites now in clinical usage for this malady for almost a century. The most potent and rapid in effect of these compounds is the volatile amyl nitrite introduced by Brunton[1] in 1867, and the next most potent is nitroglycerin first administered for angina pectoris by Murrell[4] in 1879. Nitroglycerin, because it is effective sublingually without being disagreeably potent and because it is more easily administered and lower in cost, has been preferred to amyl nitrite. While both of these rapidly acting nitrites afford relief during the acute anginal episode, they are of limited value for the prevention of attacks. Thus, when angina occurs at frequent or unpredictable intervals, the short duration of action of these drugs precludes their use in prophylaxis. Consequently, longer acting nitrites have gained popularity in recent years in an effort to reduce the severity and frequency of such episodes. With the same objective in view, some have sought to prolong the action of nitroglycerin by means of a sustained-action oral preparation. Unfortunately, the tablet so designed (Nitroglyn) was found by our group[17] to exert little influence upon the electrocardiographic response to measured exercise. Indeed, even in massive dosage the results with this preparation were often unimpressive. From these findings, therefore, it must be concluded that nitroglycerin is inactivated in some way in the gastrointestinal tract and that for clinical response the dosage by this route must be many times larger than the usual sublingual one.

Of the long-acting nitrites, pentaerythritol tetranitrate, triethanolamine trinitrate biphosphate and, more recently, erythrol tetranitrate have commanded attention (Fig. 1). Previous observations in our laboratory employing exercise-electrocardiographic tests have shown that triethanolamine trinitrate biphosphate, even in large doses (6.0 mg.), was ineffective in all patients studied by this technique[17]. From similar evaluations based primarily on exercise tolerance tests, Riseman, Altman and Koretsky[5] also concluded that the vasodilating action of this drug, by the oral route, is comparatively weak. They did observe, however, that the agent was much more effective when administered sublingually, although its usefulness by this route was frequently limited by stomatitis. In like manner, these authors noted that erythrol tetranitrate has relatively weak vasodilator properties when swallowed but behaves like nitroglycerin and "is one of the most effective vasodilators available when ad-

ministered sublingually." On the other hand, although we[17] have found pentaerythritol tetranitrate orally in a dosage of 20 mg., or more, to be uniquely effective in the majority of our patients, Riseman, Altman and Koretsky[5] have reported the drug of definite but moderate value sublingually or orally in but a small percentage of their treated cases. The present study was, therefore, undertaken to test the clinical and electrocardiographic responses to erythrol tetranitrate by the sublingual or buccal route in patients with established coronary disease, and to compare the results of exercise tests with those observed in some of the same patients while receiving pentaerythritol tetranitrate therapy.

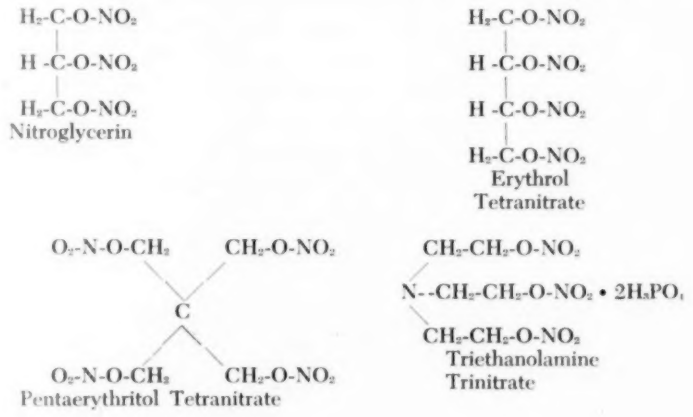

Fig. 1.—Graphic chemical formulas of nitroglycerin and other nitrites in current use.

Material and Method. The 58 patients selected for this study all presented classical symptoms of angina pectoris which routinely responded to both the prophylactic and therapeutic administration of nitroglycerin. In all cases, the diagnosis had been clearly established by the patient's history and, in more than one-half of the cases, electrocardiographic confirmation of coronary disease had also been obtained. All of the patients had been under observation for more than one year and had received various medicaments in an attempt to improve their pain experience. In all instances, the pattern of daily nitroglycerin requirements and anginal episodes was clearly established before undertaking the present study. Eleven of the 58 patients had sustained previous myocardial infarction. Fifty patients were male and 8 female. The ages ranged from 41 to 65 years.

1) EFFECT ON ANGINAL PAIN. A record of the pain experience was kept in each instance by a notation at bedtime as to whether symptoms were the same as usual, unusually severe, exceptionally mild, or completely absent. Each of the patients was treated with a separate course of erythrol tetranitrate* (15 mg.) and a matching placebo. The tablet was administered sublingually or in the buccal pouch 3 times daily after meals in successive courses of 2 weeks each. The first

*The tablet of erythrol tetranitrate originally made available (Burroughs Wellcome) had been "compressed" in order to insure slow disintegration in the buccal cavity with the aim of prolonging therapeutic activity. Although this preparation usually required from one to one and one-half hours in contact with the oral mucosa for disintegration, in a large number of patients the tablet remained unaltered for many hours or caused troublesome stomatitis. Consequently, a new rapidly-disintegrating tablet, requiring approximately 5 to 20 minutes for absorption, was supplied to replace the original preparation, and the former has been used exclusively in the present study.

medication prescribed was invariably a placebo.

2) EFFECT ON RESPONSE TO EXERCISE. In order to determine the modifying influence of the preparations under study on the electrocardiographic response to standard exercise, the Master two step test was employed in 18 carefully selected patients. In each of these, a relatively constant positive response was reproducible in control tests recorded from day to day. In addition, favorable electrocardiographic response could be obtained in each instance by the sublingual administration of nitroglycerin immediately preceding the test. There was no adherence to a "single" or "double" test as delineated by Master[3]. The number of ascents and descents of the two-step staircase was individualized according to the response and kept constant for each patient. Electrocardiographic records were obtained by this means in all 18 patients while receiving either placebo or erythrol tetranitrate (15 mg.). One or the other of these agents was administered sublingually in a single dose after breakfast on consecutive mornings 5 minutes to 4 hours before the performance of the test. In 8 patients, the results were also compared with those observed following the administration of pentaerythritol tetranitrate orally in doses of 20 to 40 mg. A total of 386 tests was obtained on the 18 patients in this study. Measurement was made of the degree of ST segment depression observed in the post-exercise electrocardiograms with each of the agents employed.

Results. 1) EFFECT ON ANGINAL PAIN. Ten of the patients in the original series discontinued erythrol tetranitrate because of troublesome side-effects and have, therefore, been excluded from the final analysis. Comparison of the responses to placebo and erythrol tetranitrate, as determined by the use of a "daily report card" in the remaining 48 patients, revealed unequivocal evidence of the therapeutic efficacy of the latter drug. Thus, during the course of placebo therapy, 36% of the patient-days were recorded as associated with "no pain" or "less pain" as compared with 74% during the course of erythrol tetranitrate therapy (Table 1). Although initially none of the patients were aware of the change in medication, this was detected subsequently in almost all instances from the alteration in pain experience or side effects, or both.

TABLE 1.—COMPARISON OF PAIN EXPERIENCE WITH PLACEBO AND ERYTHROL TETRANITRATE EVALUATED BY "DAILY REPORT CARD" IN 48 PATIENTS WITH ANGINA PECTORIS

		Percentage of Days in Which Cardiac Pain was Reported as			
Agent	*Total No. days Reported*	*Same as Usual*	*Less than Usual*	*More than Usual*	*None at All*
Placebo	670	53.0	32.8	11.0	3.2
ETN	667	22.0	51.3	4.0	22.7

The most troublesome symptom with erythrol tetranitrate was headache, the nature of which was similar to but more severe and protracted than that experienced after nitroglycerin. Of the 58 patients for whom the drug was originally prescribed, 23 complained of this disturbing side-effect. In 10 the headache was so severe that the drug had to be discontinued even after trial with smaller doses. In 6 patients, however, headache became less troublesome or disappeared when dosage was reduced from 15 mg. to 7.5 mg., and in 4 of these, the larger dosage was later resumed without difficulty. In the remaining 7 patients, headache gradually disappeared without alteration in dosage as tolerance to the drug developed. Six patients experienced

"light-headedness" or dizziness, and 9 patients complained of an unpleasant burning sensation in the buccal cavity as a result of the local action of the drug.

2) EXERCISE-ELECTROCARDIOGRAPHIC TESTS. Careful measurement of the ST segment depression after exercise disclosed that erythrol tetranitrate exerted a marked modifying influence on the electrocardiographic response in 15 of the 18 patients tested. The magnitude of the response was comparable to that following nitroglycerin in the same subjects, but the duration of action was considerably longer, commencing in about 5 minutes after the drug was placed under the tongue and persisting for 1 to 2 hours (Fig. 2). In 3 of the 18 patients, the dose of erythrol tetranitrate was reduced to 7.5 mg. because of headache. In all 3, the latter was avoided by this means without appreciable loss of therapeutic effect.

In 8 patients, the exercise-electrocardiographic responses to erythrol tetranitrate (ETN), sublingually, were compared with those observed following the administration of pentaerythritol tetranitrate (PETN) orally in doses of 20 to 40 mg. Although the magnitude of the responses to these drugs was similar, the time of onset and duration of action differed markedly. Thus, with ETN administered sublingually, favorable response was observed in 5 to 10 minutes and persisted for 1 to 2 hours. In sharp contrast, PETN orally pro-

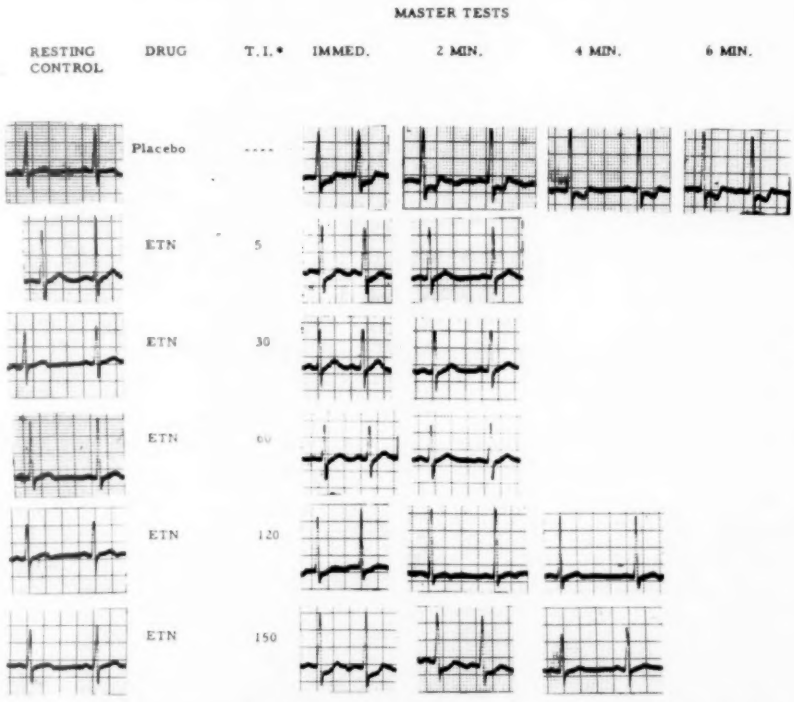

Fig. 2.—Master test responses (lead V_4) obtained in a patient with angina pectoris receiving placebo or erythrol tetranitrate (15 mg.) sublingually at various intervals before exercise. *T.I., time interval (minutes) between medication and beginning of test.

duced favorable effects only after an hour or longer, but the duration of its action was 4 to 5 hours, a span more than twice that of ETN (Figs. 2 to 4). On the other hand, a sublingual tablet containing PETN (10 mg.) and nitroglycerin (gr. 1/200) was found to have little more than the anticipated nitroglycerin effect even when 2 or 3 tablets were placed under the tongue simultaneously. Thus, little response could be elicited with this preparation after 40 to 60 minutes. Consequently, PETN sublingually appears to have relatively brief vasodilator effect immediately following administration and cannot classify as a long-acting nitrite by this route. It is concluded, therefore, that in prophylactic management PETN is far more effective when administered orally than sublingually, and that the reverse is true for ETN as ably demonstrated by Riseman, Altman and Koretsky[5].

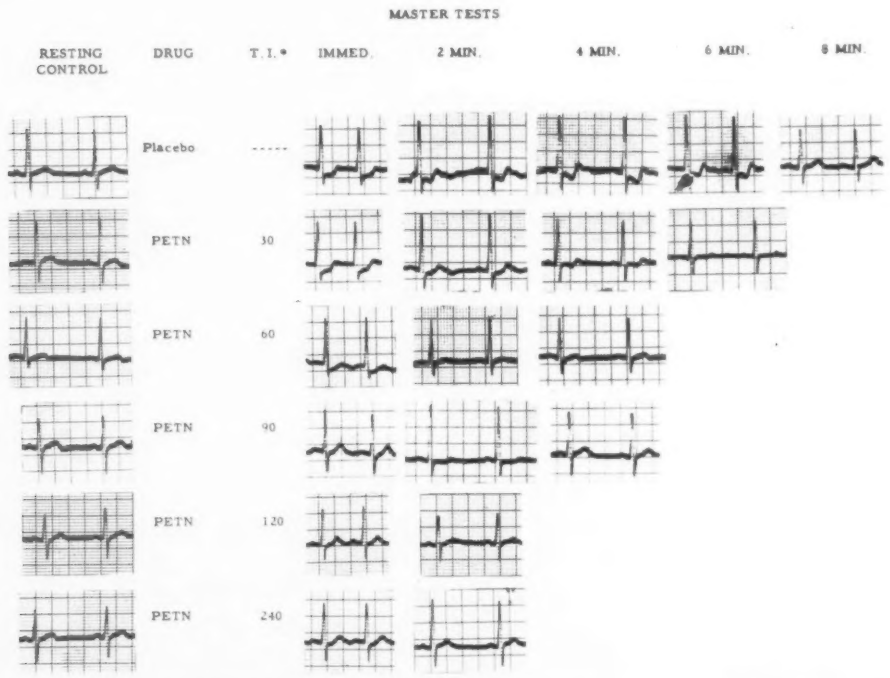

Fig. 3.—Master test responses (lead V_4) obtained with placebo or pentaerythritol tetranitrate (20 mg.) administered (orally) at various intervals before exercise. (Same patient as in Fig. 2.)
*T.I., time interval (minutes) between medication and beginning of test.

Discussion. From the vantage point of an observer who has used the techniques of drug evaluation embodied in the present report over a period of the last 15 years (Russek[6,7,8], Russek *et al.*[10,11,12,13,14,16,17]), erythrol tetranitrate, by the sublingual or buccal route, appears to be worthy of a place in the therapy of patients with angina pectoris. One 15 mg. tablet, placed under the tongue, generally produced an effect equal to that of 1/150 grain of nitroglycerin, but the duration of action was at least fourfold. Thus, the response to a tablet of ETN sublingually paralleled that of 4 to 6 nitroglycerin

tablets administered singly at 20- to 30-minute intervals by the same route.

The main objection to the use of erythrol tetranitrate was the severe throbbing headache observed in a relatively high percentage of the patients treated. In some cases, this could be avoided by starting with half a tablet and subsequently increasing to full dosage after a week or two. Unfortunately, some patients are intolerant to even small doses of the drug, and, in them, it had best be avoided. For the many patients who show no significant side-effects, erythrol tetranitrate may be singularly useful. Because of its rapid action, usually within 5 to 10 minutes after sublingual administration, this agent may confer protection for an hour or two after meals when anginal attacks are most prone to occur. For the same reason it may be used like nitroglycerin before contemplated exertion or excitement when more prolonged prophylaxis is desired. Because of the potency of the drug, it appears wise to commence with a dosage of 7.5 mg. until the individual response has been determined, and thereafter to increase the dose to 15 mg. if tolerated. One patient in the present series experienced a paradoxic effect from the use of ETN similar to that which we[15] have reported with nitroglycerin. Thus, the administration of a 15 mg. tablet sublingually consistently produced typical chest pain, while smaller doses of the drug were well tolerated without symptoms.

With pentaerythritol tetranitrate, the lag of an hour or more before significant response usually leaves the patient unprotected during the vulnerable period following the ingestion of food unless the time of administration is designed to avoid this pitfall. This may be accomplished by giving PETN one-half to one hour before meals. Indeed, administration after food has been shown to attenuate the response probably as the result of inactivation in the gastrointestinal tract or interference with absorption[17]. Despite unequivocal benefits observed in electrocardiographic tests, some physicians have obtained favorable clinical responses to PETN in only a few patients with angina pectoris. This seeming paradox can be explained on the following grounds:

1. The dose of PETN initially recommended and widely employed was only 10 mg., a dosage found to be inadequate in most instances.

2. PETN is still taken after meals by many patients, contrary to advice

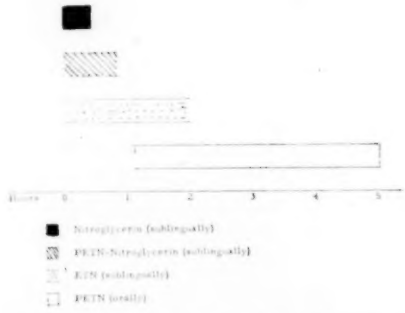

Fig. 4.—Time of onset and duration of action of nitroglycerin, pentaerythritol tetranitrate, erythrol tetranitrate and PETN-nitroglycerin combination.

or because so instructed. Evidence appears clear that therapeutic response to the drug is markedly diminished with administration after food[17].

3. In the manner commonly prescribed, that is, three times a day before meals, the patient is unprotected by the drug during periods of the day when anginal episodes are most prone to develop. Thus, with the first tablet taken at approximately 8:00 a.m. before breakfast, there is no protection on arising or in travel to work since significant response cannot become manifest before 9:00 or 9:30 a.m. Obviously the high percentage of anginal attacks known to occur during this early morning period are uninfluenced by such therapy. Similarly, inasmuch as the span between lunch and dinner is usually 6 hours, a gap is produced not only by "overrunning" the duration of activity of the noonday pill (4 to 5 hours), but also by the lag in action following the evening dose. As a consequence, the patient is again unprotected during a time of the day when anginal episodes are most prone to occur, that is, returning home from work and after the evening meal. It is little wonder, therefore, that PETN has been found ineffective in many patients with relatively mild to moderate angina in whom attacks without treatment are seen primarily during the periods when this drug offers no protection.

The deficiency in action of PETN may be corrected by adjustment in the time-dosage schedule of the drug or by complementing its action with that of other agents. Thus, this may be accomplished by the administration of PETN one hour before meals with the addition of a mid-afternoon dose at approximately 3:30 p.m. An alternative method, perhaps more convenient for the patient, might be found by administration of the drug three times daily shortly before meals with the concomitant use of ETN sublingually on arising and at 5:00 p.m. on leaving work. From electrocardiographic tests, the latter appears feasible since the effects of these agents are more complementary than they are parallel (Fig. 4). The combined use of these agents in the manner suggested affords the best prophylactic management possible today with drugs currently available. In this regard, experience with various sustained-action preparations of PETN and of other vasodilators has proved that clinical response to these agents falls far short of theoretical predictions.

Summary. Clinical evaluation of erythrol tetranitrate administered sublingually in 58 patients with angina pectoris has clearly demonstrated the therapeutic effectiveness of this agent. Exercise-electrocardiographic tests obtained in 18 of these cases have shown that the magnitude of the response is comparable to that following nitroglycerin while the duration of action is considerably longer, persisting for one to two hours. A serious drawback in the routine use of ETN sublingually in the treatment of angina pectoris is the frequency with which headache is encountered. Forty per cent of the patients in the series suffered from this side-effect, and in almost half of these therapy had to be discontinued. In the remainder, however, headache disappeared as tolerance to the drug developed or when dosage was reduced from 15 mg. to 7.5 mg. It is, therefore, recommended that treatment be initiated with the lower dosage until patient response can be determined.

The magnitude of the response to pentaerythritol tetranitrate in 8 patients was similar to that observed with erythrol tetranitrate sublingually, but the time of onset and duration of action of the respective drugs differed markedly. PETN orally produced favorable

effects only after an hour or more following ingestion, but the duration of its action was more than twice that of ETN. In contrast, PETN sublingually was found to have an immediate but relatively brief vasodilator effect.

Pentaerythritol tetranitrate orally is superior to erythrol tetranitrate sublingually in its relative freedom from troublesome side-effects and in its more prolonged action. Its chief disadvantage, however, is the lag in activity inherent in its use. Erythrol tetranitrate because of its rapid onset of effect is, like nitroglycerin, ideally suited for prophylactic administration prior to contemplated exertion or excitement. For this purpose one 15 mg. tablet of ETN sublingually has the effect of 4 to 6 nitroglycerin tablets administered singly at 20- to 30-minute intervals by the same route.

Pentaerythritol tetranitrate has been associated with disappointing results in some cases because of 1) inadequate dosage, 2) administration after food, and 3) time-dosage schedules which have left the patient unprotected during the most vulnerable periods of the day. Suggestions are made for correcting these inadequacies and for combining erythrol tetranitrate and pentaerythritol tetranitrate in a regimen designed to give continuous prophylaxis.

ACKNOWLEDGMENT: This study was supported by a grant from Burroughs Wellcome & Co.

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SUMMARIO IN INTERLINGUA

Evalutation del Nitritos in le Tractamento de Angina de Pectore

Le evalutation clinic del effectos de administrationes sublingual de tetranitrato de erythritol in 58 patientes con angina de pectore ha clarmente demonstrate le efficacia de iste agente. Electrocardiogrammas obtenite post exercitio in 18 de iste casos ha monstrate que le magnitude del responsa es comparabile a illo

resultante de nitroglycerina durante que le persistentia del action es multo plus extense, usque a un o duo horas. Un serie obstaculo al uso routinari de tetranitrato de erythritol in administrationes sublingual in angina de pectore es le frequentia del effecto lateral de mal de capite. Quaranta pro cento del patientes in le presente serie suffreva de iste effecto lateral, e in quasi un medietate de illes le therapia debeva esser interrumpite. Tamen, in le alteres, le mal de capite dispareva quando le tolerantia pro le droga se disveloppava o quando le dosage esseva reducite ab 15 a 7,5 mg. Per consequente, il es recommendate que le tractamento es initiate al dosage plus basse usque le responsa del patiente pote esser determinate.

Le magnitude del responsa a tetranitrato de pentaerythritol in 8 patientes esseva simile a illo observate con tetranitrato de erythritol in administrationes sublingual, sed le tempore del declaration del efficacia e le duration del action differeva marcatemente inter le duo drogas. Tetranitrato de pentaerythritol in administrationes oral produceva effectos favorabile solmente un hora o plus post le ingestion, sed le duration del action esseva plus que duo vices illo de tetranitrato de erythritol. Del altere latere, il esseva constatate que tetranitrato de pentaerythritol in administration sublingual habeva un immediate ben que relativemente breve effecto vasodilatatori.

Tetranitrato de pentaerythritol per via oral es superior a tetranitrato de erythritol per via sublingual a causa del facto que illo es relativemente libere de adverse effectos lateral e que su action es plus perdurative. Su principal disadvantage es le retardo del declaration de su activitate. Tetranitrato de erythritol—a causa del rapiditate del declaration de su effecto—es, como nitroglycerina, idealmente appropriate al uso prophylactic ante un expectate effortio o excitation. Pro iste objectivo, un tabletta de 15 mg de tetranitrato de erythritol per via sublingual ha le effecto de 4 a 6 tablettas de nitroglycerina administratè un post un a intervallos de 20 a 30 minutas per le mesme via.

Tetranitrato de pentaerythritol ha essite associate con resultatos disappunctante in certe casos a causa de (1) un inadequate dosage, (2) le administration post le ingestion de alimentos, e (3) un horario de administration que lassava le patiente sin protection durante le plus vulnerabile periodos del die. Es presentate suggestiones que permitte le correction de iste inadequacias. Es etiam suggerite le uso combinate de tetranitrato de erythritol e de tetranitrato de pentaerythritol in un regime visante a provider un prophylaxe continue.

THE CARDIOVASCULAR-RESPIRATORY EFFECTS OF A NEW XANTHINE DERIVATIVE IN CHRONIC PULMONARY EMPHYSEMA AND IN MITRAL STENOSIS*

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Xanthine compounds have been extensively investigated for their action on both circulation and pulmonary ventilation (Dulfano *et al.*[5], Segal *et al.*[9], Storstein, Helle and Rokseth[11], Werkö and Lagerlof[12]). Modern techniques in the study of pulmonary function and pulmonary circulation have produced, in recent years, a renewed interest in the physiological aspects of pulmonary disease, and have contributed important information on pulmonary circulation and the various types of pulmonary hypertension.

This study was undertaken to determine the effects of a new xanthine derivative, 7-(ω-piperidino-butanon-2-yl-[1]) theophyllin (X-D)† on pulmonary ventilation and circulation in cases with chronic pulmonary emphysema and mitral stenosis.

Material and Methods. Nineteen patients were studied at rest and 30 minutes after administration of 0.10 to 0.20 gm. of X-D into the pulmonary circulation during cardiac catheterization. Eight of these patients were suffering from moderately advanced to advanced chronic pulmonary emphysema, and the remaining 11 patients had "pure" mitral stenosis later confirmed at operation. Catheterization was performed following the technique of Cournand and Ranges[4]. A mild barbiturate (Nembutal 0.05 to 0.10 gm.) was administered to all mitral stenosis patients and 0.25 to 0.50 gm. of chloral hydrate to 6 patients with pulmonary emphysema. No premedication was employed in 2 cases of advanced pulmonary emphyema with CO_2 retention. Simultaneous blood samples were obtained under anaërobic conditions from the radial and pulmonary artery, while the patient inspired collected air of known composition through a Collins J valve during a 5-minute period. The number of respirations were counted and expired air was collected in a Douglas bag. Simultaneous pressures from radial and pulmonary artery were recorded at rest, after placebo administration, immediately after injection of X-D into the pulmonary artery and at 15-minute intervals.

The Fick principle was applied to determine cardiac output at rest, and at the end of 30 minutes after injection of the drug. Blood samples were analyzed for CO_2, O_2 and blood hemoglobin O_2-carrying capacity. Arterial blood pH was determined at room temperature and corrected to 38° C. Arterial pCO_2 was obtained with the Singer and Hastings[10] nomogram. Expired air was analyzed in the micro Scholander apparatus.

*This study was supported in part by a grant from Hoffman-LaRoche and by donations from Roberto Maduro and Guillermo Alamilla.

†Supplied by Hoffman LaRoche: Research name Ro-1-8239.

Physiological dead space was determined using the Bohr formula[2], assuming alveolar pCO_2 identical with arterial pCO_2, and corrected by subtracting the dead space of the equipment (90 ml.). The VD:VT ratio was corrected in the same manner. The formulas used to determine total pulmonary resistance, arteriolar pulmonary resistance, and work against resistance of the right and left ventricle are those of Gorlin and associates[6]. The results have been studied statistically by means of Student's "t" test. Spirometric studies were done previously in all patients. In all patients with chronic pulmonary emphysema, spirometry was repeated 30 minutes after intravenous administration of 0.10 gm. of X-D. In 5 cases of chronic pulmonary emphysema oxygen 100% was given for 15 minutes, 30 minutes after administration of X-D, and blood samples were obtained in the same manner.

In a control group of 8 chronic pulmonary emphysema cases, spirometry, residual volume, total lung capacity, and arterial blood studies were done at rest and 30 minutes after intravenous administration of 0.10 gm. of X-D and on separate occasions retested in the same manner at rest and 30 minutes after intravenous administration of 0.25 gm. of aminophylline.

Results. A comparison of the effects produced by 0.10 gm. of X-D and 0.25 gm. of aminophylline on lung volumes, spirometry, arterial blood and ventilation showed no statistical differences. However, in some cases X-D had a more pronounced action even though the dose was one-half that of aminophylline. Also, minor side reactions, discomfort and dizziness were more frequent with aminophylline.

SECTION 1.—PULMONARY FUNCTION.

TABLE 1.

SECTION I

Pulmonary function studies during cardiac catheterization. Control values are compared with values obtained 30 minutes after administration of 0.10 gm. X-D into the pulmonary artery.

	Pulmonary Emphysema		*Mitral Stenosis*	
	Average of % change	*p*	*Average of % change*	*p*
V_D (ml.)	15.6 % decrease	0.05	14.3 % decrease	–
$\dot{V}_A$ (l./min.)	12.3 % increase	0.05	15.1 % increase	–*
V_D/V_T	14.2 % decrease	0.02	16.6 % decrease	0.02
pCO_2 (mm.Hg)	6.7 % decrease	–	12.7 % decrease	0.005
Hb capacity (vol. %)	2.3 % increase	–	0.8 % decrease	–
SaO_2	2.3 % decrease	0.001	0.8 % decrease	–
$S\bar{v}O_2$ (%)	3.9 % decrease	–	0.8 % increase	–
$\dot{V}O_2$ (ml./min.)	3.0 % increase	–	2.6 % increase	–*
pH (units)	0.3 % increase	0.05	0.6 % increase	1.005
$\dot{V}$ (L./min.)	1.0 % decrease	–	0.2 % increase	–
f	2.3 % increase	–	4.4 % increase	–
RQ	0.05 % increase	–	2.8 % decrease	–*
Pulse (beats/min.)	4.3 % increase	–	2.0 % increase	–

SECTION II

Cardiac catheterization. Control pressures from Radial and Pulmonary Artery are compared with those obtained 15 minutes after administration of 0.10 gm. X-D into the pulmonary artery.

	Pulmonary Emphysema		*Mitral Stenosis*	
	Average of % change	*p*	*Average of % change*	*p*
Pul. Artery:				
Systolic pres.	12.6 % decrease	–	13.6 % decrease	0.05
Diastolic pres.	9.6 % decrease	–	13.2 % decrease	0.05
Radial Artery				
Systolic pres.	5.0 % decrease	–	8.2 % decrease	0.01
Diastolic pres.	5.3 % decrease	–	16.6 % decrease	0.001

SECTION III

Control values are compared with those obtained 30 minutes after administration of X–D into the pulmonary artery.

	Pulmonary Emphysema		*Mitral Stenosis*	
	Average of % change	*p*	*Average of % change*	*p*
Pulmonary Artery				
Systolic pres.	15.9 % decrease	0.05	9.7 % decrease	–
Diastolic pres.	11.0 % decrease	–	6.9 % decrease	–
Mean pres.	13.5 % decrease	–	3.9 % decrease	–
Pulmonary "capillary"				
Mean pres.	25.7 % decrease	–	16.4 % decrease	
Radial Artery				
Systolic pres.	1.1 % decrease	–	7.8 % decrease	0.05
Diastolic pres.	3.5 % decrease	–	14.5 % decrease	0.01
Mean pres.	3.9 % decrease	–	14.8 % decrease	0.02
Total Pulm. Resist.	3.9 % decrease	–	4.1 % decrease	–
Arteriol. Pulm. Resist.	6.1 % decrease	–	37.3 % increase†	–
Systemic Resistance	8.1 % decrease	0.025	7.9 % decrease	–
Cardiac Output (l/min)	4.5 % increase	–	5.2 % increase	–
A–V Difference	2.9 % increase	–	0.5 % decrease	–
Work of Left Vent.	2.9 % increase	–	1.8 % decrease	–
Work of Right Vent.	0.9 % increase	–	3.7 % increase	–

*All mitral stenosis cases show an increase in alveolar ventilation. In one case the increase is very large and out of the norm. If this case is eliminated, the increase in alveolar ventilation is statistically significant. Elimination of this case results in a reduction of oxygen consumption to 1.8% and RQ. becomes 1.2% reduction.

†If two cases which started with very low control values, and exhibited a large percentage increase but only up to a value within the normal range, are omitted, then arteriolar pulmonary resistance is found to be *decreased* in mitral stenosis.

V_D = Physiological dead space
$\dot{V}_A$ = Alveolar ventilation (in liters per minute)
V_D/V_T = Physiological dead space: Tidal volume ratio
$PaCO_2$ = Carbon dioxide tension in arterial blood (in mm. Hg)
Hb capacity = Blood hemoglobin oxygen carrying capacity (volumes %)
SaO_2 = Arterial oxygen saturation
SvO_2 = Mixed venous blood oxygen saturation
$\dot{V}O_2$ = Oxygen consumption (ml. per minute)
$\dot{V}$ = Pulmonary ventilation (Liters per minute)
f = Frequency of respiration
RQ = Respiratory quotient

In both emphysema and mitral stenosis, the ratio of physiological dead space to tidal volume was significantly decreased and arterial blood pH significantly increased. Alveolar ventilation was significantly increased in pulmonary emphysema cases. Although all cases of mitral stenosis showed an increase in alveolar ventilation 30 minutes after administration of X-D, this increase was not statistically significant. This is due to the fact that in one case of mitral stenosis, a considerable alveolar hyperventilation occurred, and determination of the standard deviation is markedly affected by one instance of marked deviation regardless of sign. If this case is omitted, the increase in alveolar ventilation becomes significant in the mitral stenosis group.

The decrease observed in physiological dead space is significant for pulmonary emphysema but not significant in mitral stenosis. Similarly, arterial oxygen saturation decreases significantly in emphysema cases but insignificantly in mitral stenosis. Table 2 shows the results of administering pure oxygen during 15 minutes to 5 cases of pulmonary emphysema, immediately after ob-

taining the 30-minute blood sample after X-D administration. The blood oxygen saturation became normal in 2 cases, while in 3 cases unsaturation persisted.

SECTION 2.—CATHETERIZATION STUDIES. There is a significant decrease in both pulmonary and systemic systolic and diastolic pressures in mitral stenosis. In emphysema, the decrease in pressure is not significant.

perfusion in areas which were well ventilated but poorly or non-perfused; and 3) both. Both bronchodilatation and pulmonary vasodilatation have been reported as actions of other xanthine compounds (Quimby, Aviado and Schmidt[7], Segal *et al.*[9]). The increased alveolar ventilation is a corollary to this action. As a result of an increase in alveolar ventilation, there is a drop in pCO_2 and this determines

TABLE 2.—EFFECT OF X-D AND THE INHALATION OF PURE OXYGEN ON ARTERIAL OXYGEN SATURATION IN 5 CASES OF PULMONARY EMPHYSEMA.

	Arterial Saturation at rest %	*Arterial Saturation 30 min. after X-D* %	*Arterial Saturation 15 min. after O_2* %
Case 1	94.1	90.7	93.1
Case 2	93.1	88.6	99.2
Case 3	93.5	93.0	92.0
Case 4	82.3	71.3	96.0
Case 5	70.1	60.3	93.0

SECTION 3. Significant decreases in pulmonary artery systolic pressure and systemic resistance were noticed in emphysema cases. These same items were insignificantly decreased in mitral stenosis patients. In these latter patients, however, there were significant decreases in systemic, systolic, diastolic and mean pressures. It should be pointed out that the decrease in pressure and resistances occurs despite the fact that in 5 out of 8 emphysema cases, the cardiac output is increased. Similarly, in the mitral stenosis group, there was a decrease in pulmonary and systemic pressures despite the fact that 8 out of 11 showed an increase in cardiac output.

Discussion. The drug apparently increases pulmonary ventilation in emphysema cases. The reduction in physiological dead space may be due to 1) An increase in ventilation in areas which were well perfused but poorly or non-ventilated; 2) an increase in

an increase in arterial blood pH. The change in $V_D:V_T$ ratio means that more inspired air reaches the alveoli in each inspiration. The reduction of this ratio indicates (Riley and Cournand[8]) that a significant proportion of alveoli have a better perfusion in relation to its ventilation.

The significant reduction in arterial oxygen saturation confirming previous observations (Barrera, Regalado and Bezos[1]) depends upon changes in alveolar ventilation: perfusion ratio throughout the lung (Comroe *et al.*[3]). Another possible explanation would be the fact that this drug opens up pathways which act as venous-arterial shunts.

When pure O_2 was given to 5 cases showing a significant drop in arterial oxygen saturation, it was completely corrected in two demonstrating that unsaturation depended on alterations of alveolar ventilation:perfusion relationships, while in 3 of them unsaturation

could not be corrected completely, thereby detecting the presence of venous-arterial communications. For the mitral stenosis group, a similar statement could be made, except that the decrease in arterial oxygen saturation is insignificant. This may be interpreted as due to the fact that the parenchymal changes in the lung of mitral stenosis are of a different nature, and probably less important than those found in advanced cases of emphysema.

Catheterization studies show a constant decrease in all pressures, pulmonary and systemic. All resistances are also reduced except pulmonary artery resistance in the mitral stenosis group. This occurs despite the fact that in mitral stenosis pulmonary artery pressure is reduced and cardiac output is increased. It can be explained as follows: Two of the cases included started with very low control values for arteriolar resistance. These 2 show a large percentage increase although the final or experimental values were still well within the normal range. Therefore, if these 2 cases are eliminated in the calculation, the arteriolar pulmonary resistance is found to be decreased in mitral stenosis.

The fact that resistances are decreased although cardiac output is increased, serves to emphasize that decreased resistance and vasodilatation have occurred. In the pulmonary circulation the "capillary" pressure is reduced, indicating that a vasodilatation is probably located in the small vessels, arterial or venous.

Summary. Eleven cases of "pure" mitral stenosis and 8 cases of advanced pulmonary emphysema were studied during cardiac catheterization, at rest and 30 minutes after intravenous administration of 0.10 to 0.20 gm. of a new xanthine derivative Ro 1-8239. The drug increases alveolar ventilation, reduces physiological dead space, arterial pCO_2, V_D:V_T ratio and increases arterial blood pH. These changes are interpreted as action on pulmonary circulation probably associated with bronchodilatation.

The drug produced a drop in systemic and pulmonary pressures at the end of 15 and 30 minutes. It decreases all resistances and increases cardiac output. These changes are due to vasodilatation, both systemic and pulmonary.

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(Interlingua on page 444)

ELECTROCARDIOGRAPHIC SIGNS OF PERICARDITIS IN TYPHOID FEVER

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ELECTROCARDIOGRAPHIC abnormalities in typhoid fever are frequent and have been reported by numerous investigators (Clerc and Levy[4], Brow[2], Chagas[3], Porter and Bloom[9], Stuart and Pullen[12], Mainzer[8], Rachmilewitz and Braun[10], Benhamou and Abou[1]). The most frequent alteration consists of flattening or inversion of the T wave, depression of the S–T segment, and disturbances in rhythm. Inflammatory-toxic (Romberg[11]) and metabolic (Rachmilewitz and Braun[10]) factors have been held responsible for the electrocardiographic changes.

This report was prompted by the finding of electrocardiographic changes of pericarditis in 3 patients with typhoid fever.

Case Reports. CASE 1. R.C., aged 16, female, student. Two weeks prior to hospitalization her temperature started rising gradually and remained high until her admission. The patient suffered from severe headache and constipation. Treatment with chloramphenicol was commenced 2 days prior to hospitalization.

On admission (June 29, 1959) the patient appeared ill and her temperature was 37.6° C. The pulse was regular at a rate of about 100 per minute. The blood pressure was 115/65 mm. Hg. The tongue was slightly coated. There were no abnormal findings in the heart and lungs. The edge of the spleen was palpable. There was no skin rash.

Laboratory examinations. Urine normal; blood count: erythrocytes 3.8 million, hemoglobin 11 gm.%, leukocytes 6,200 per c.mm. The sedimentation rate was 55/96 mm. (Westergren). Liver function tests were normal. Blood, urine and stool cultures grew no typhoid bacilli. The Widal reaction was positive at a titer of 1:400. Roentgenogram of the chest was normal.

On administration of 1.0 gm. chloramphenicol daily the patient's condition improved within several days, her temperature returning to normal after 2 days.

Electrocardiographic study (Fig. 1). On the first day of hospitalization (June 29, 1959) the electrocardiogram showed: sinus rhythm, 100 per minute; P–Q interval 0.14 second; QRS normal; S–T segment elevated in chest leads V_2–V_5. The T waves were upright in all leads except aVR, and notched in V_2. A series of electrocardiograms performed thereafter showed a gradual trend towards the pattern in part B of Fig. 1 (July 13, 1959). The main change was an inversion of the T waves in the chest leads, while the S–T segment was still slightly above the isoelectric line. This electrocardiogram remained unchanged following the intravenous injection of 50 mg. of niacin and the subsequent administration of 500 mg. of niacin daily for 3 days.

COMMENT. The clinical course in this case was typical of typhoid fever and the positive Widal reaction confirmed the diagnosis. Following defervescence, the classical electrocardiographic signs of pericarditis were observed. These persisted more than 2 weeks, the last electrocardiogram still showing the characteristic changes. There were no clinical and roentgenographic signs of pericarditis during the whole period of hospitalization.

CASE 2. A.L., aged 30, female, mother of 2 children, housewife. The family and past history were irrelevant. A month prior to hospitalization the patient began to suffer from headache, pain in the epigastrium and vomit-

ing after meals. The temperature rose to 39° C., and remained high during the subsequent 2 weeks, following which the patient was given 1.0 gm. chloramphenicol daily for 3 days. During this treatment the temperature fell to normal and remained so for a week. Five days prior to admission the temperature rose again, the headache and pain in the epigastrium increased, and pains in the flanks appeared.

On admission (November 2, 1958) the patient appeared intoxicated and flushed. The temperature was 40.2° C., the pulse regular at 108 per minute, the blood pressure 100/80 mm. Hg. The tongue was coated, the pharynx inflamed. There were no abnormal findings in the lungs. The heart sounds were clear; no murmurs were heard. The liver was felt 2 cm. below the costal margins and was tender; the spleen was not felt. There were no rose-spots.

Laboratory examinations. Urine analysis showed albumin ++, increased urobilinogen, a few granular cylinders, leukocytes and erythrocytes and many epithelial cells. Eight urine cultures were sterile. Blood count: erythrocytes 4.7 million, hemoglobin 12.2 gm.%, leukocytes 8,000 per c.mm., erythrocyte sedimentation rate 62/93 (Westergren). Seven stool cultures grew no typhoid bacilli; no ova and parasites were found. A blood culture grew *Salmonella typhosa*. The titer of the Widal reaction rose from 1:100 to 1:800 in the course of the disease. Liver function tests were impaired: cephalin-cholesterol flocculation +++, thymol flocculation +, alkaline phosphatase 10.0 Bodansky units. Blood urea was 28 mg. per 100 ml. The Wassermann test was negative.

The patient was started on 3.0 gm. chloramphenicol daily during the first 4 days, followed by smaller doses until the end of hospitalization (November 22, 1958). The temperature fell to normal within 5 days. All subjective complaints disappeared, as did the abnormal urinary findings, and the liver function tests became normal.

Electrocardiographic study (Fig. 2). On the first day of hospitalization (November 2, 1958) the electrocardiogram showed: sinus rhythm, 110 per minute; P–Q interval 0.14 second; QRS complex, normal; S–T segment slightly depressed in leads II, III, aVF and the left precordial leads; T wave flat or inverted in all leads. A week later (November 9, 1958), 3 days after the temperature had returned to normal, the electrocardiogram showed signs of pericarditis. There was sinus rhythm of 80 per minute; P–Q interval and QRS complex were normal; the S–T segment was elevated above the isoelectric line in leads I, II, III, aVF and V_3 to V_6, and slightly depressed in aVR. The T wave was upright in all leads except in aVR and V_1, where it was inverted, and in aVL, where it was flat. A similar pattern persisted 4 days, as shown by daily electrocardiograms. No pericardial friction rub was heard during this period, nor did the patient experience any symptoms of pericarditis. Roentgenogram of the chest showed no abnormal findings. On November 15, 1958, the electrocardiogram was normal. No treatment other than chloramphenicol had been given.

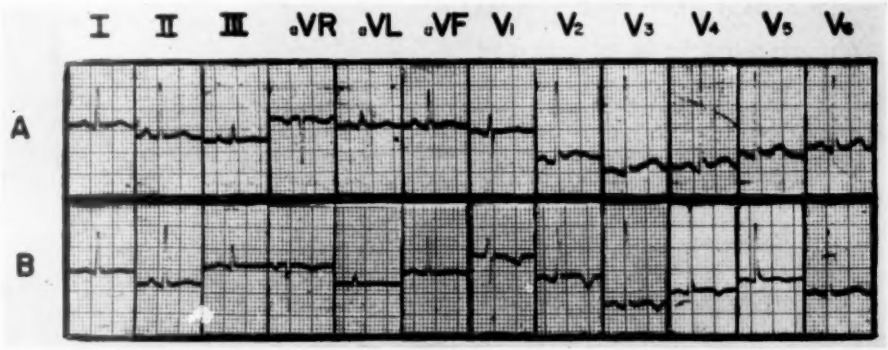

Fig. 1.—*A*) electrocardiogram on first day of hospitalization (June 29, 1959). Note S–T elevation in chest leads V_2-V_5.

B) 15 days later (July 13, 1959) the T wave became inverted in leads V_1 to V_5, while the S–T segment was still slightly above the isoelectric line.

COMMENT. This patient suffered from a relapse of typhoid fever, which appeared a week after discontinuation of a 3-day course of chloramphenicol, which had brought the temperature down to normal. The diagnosis was proven by a positive blood culture and a rising Widal titer. The disease was complicated by marked liver damage and febrile nephrosis. The electrocardiographic changes during the febrile stage consisted mainly of flattening and inversion of the T waves. After the temperature fell to normal, the electrocardiogram showed high take off and elevation of the S–T segment, characteristic of pericarditis, which persisted 4 days. No other subjective or objective signs of either pericarditis or myocarditis were present. The electrocardiographic changes disappeared spontaneously with no treatment other than chloramphenicol being given.

CASE 3. S.T., aged 25, female, mother of one healthy child. Her past history was unremarkable. Six days prior to admission, the patient began to feel severe headache and malaise. Three days later the temperature was found to be 38° C. Pains in the right hypochondrium appeared and persisted until hospitalization (July 29, 1956).

Physical examination revealed malnutrition, a general appearance of intoxication, temperature 40° C., pulse 96 per minute and regular, blood pressure 120/70 mm. Hg, tongue with coated margins. Lungs and heart were normal, except for a grade I–II systolic murmur over the whole precordium. The liver was felt 3 cm. below the costal margin, and was tender; the spleen was felt 2 cm. and was soft. No other pathological findings were noted.

Laboratory examinations. Urine showed albumin ++, urobilinogen increased, a few leukocytes and erythrocytes; 3 cultures were sterile. Blood count: erythrocytes 3.8 million, hemoglobin 10.4 gm.%, leukocytes 4,750 per c.mm. Erythrocyte sedimentation rate 16/43 mm. Blood, urea, glucose, proteins and liver function tests were all normal. One blood culture grew *Salmonella typhosa*. Three stool cultures grew no typhoid bacilli.

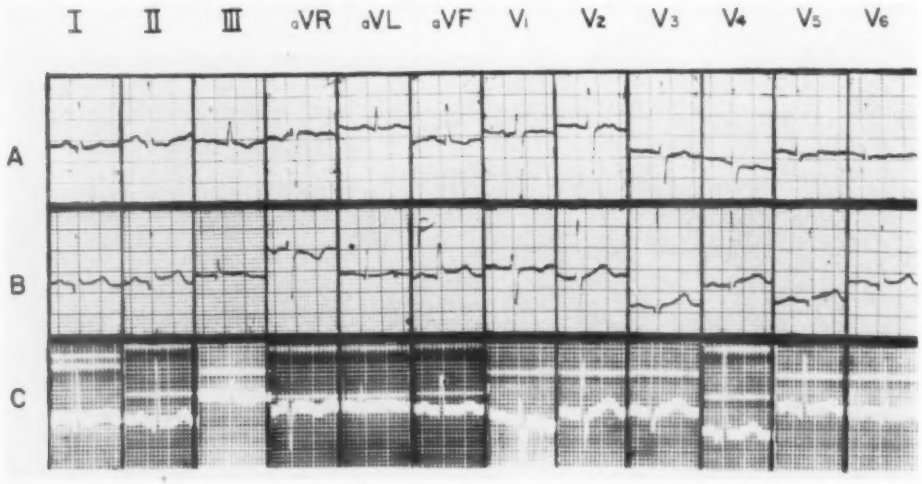

Fig. 2.—*A*) electrocardiogram on first day of hospitalization (November 2, 1958). Note slight depression of S–T segment in leads II, III, aVF and left precordial leads; the T wave is flat or inverted in all leads.

B) a week later (November 9, 1958) the S–T segment was elevated as much as 3 mm. above the isoelectric line in leads I, II, III, aVF and V_{3-6}.

C) 6 days later (November 15, 1958) the electrocardiogram was normal.

The patient was treated with 1.5 gm. chloramphenicol daily. The temperature became normal after 5 days and she was discharged from hospital after 2 weeks.

Electrocardiographic study (Fig. 3). On the first day of hospitalization the electrocardiogram showed: sinus rhythm, 107 per minute, P–R interval 0.16 sec., QRS complex normal, S–T segment depressed in precordial leads V_{3-6}, T wave isoelectric or inverted in all leads. Six days later (July 3, 1956), when the temperature had become normal, the electrocardiogram showed: sinus rhythm, 70 per minute, P–R interval and QRS complex normal; the S–T segment showed a high take off in leads I, II, III, aVF and V_{3-6}; in aVR it was below the isoelectric line. The T wave was upright in all leads except in aVR and V_1. This pattern, characteristic of pericarditis, disappeared after 5 days with no special treatment. No pericardial friction rub was heard and the roentgenogram of the heart showed no abnormal findings. The patient had no clinical signs of pericarditis.

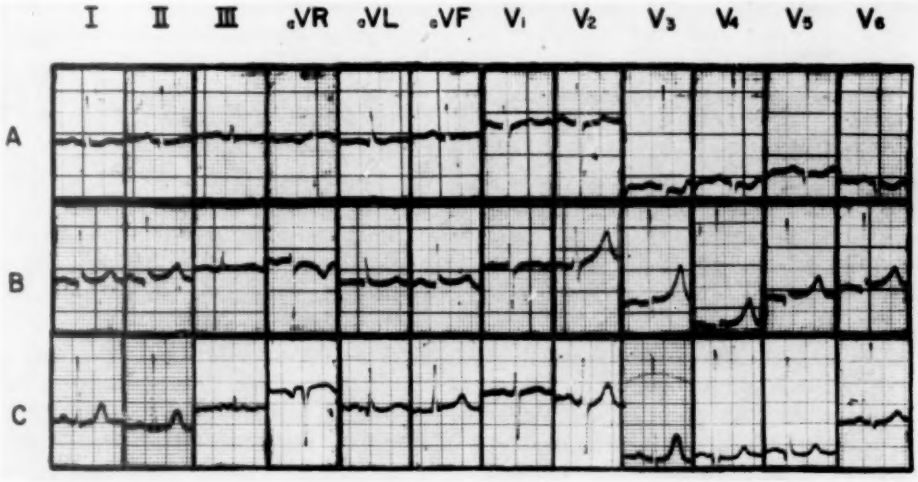

Fig. 3.—*A*) electrocardiogram on the first day of hospitalization (July 29, 1956). Note slight depression of the S–T segment in the precordial leads V_{3-6}, and flat or inverted T waves in most leads.

B) 6 days later (August 4, 1956) the S–T segment showed a high take off in leads I, II, III, aVF and V_{3-6}.

C) 5 days later (August 9, 1956) the electrocardiogram was normal.

COMMENT. This was a typical case of typhoid fever. The electrocardiographic changes during the febrile stage were similar to those in the second case, depression of the S–T segment and flattening or inversion of the T waves. Following defervescence a transitory electrocardiographic pattern of pericarditis appeared, unaccompanied by other evidence of pericarditis.

Discussion. Morphologic changes in the myocardium ("toxic myocarditis") in typhoid fever were observed long ago and described in 1891 by Romberg[11]. More recently, however, their frequency was questioned (Friedberg[5]). The changes consist of cloudy swelling of the muscle fibers, and less frequently, interstitial infiltration with round and polymorphonuclear cells.

Electrocardiographic changes in typhoid fever, indicating myocardial involvement, are much more frequent and consist mostly of flattening or inversion of the T wave, depression of the

S–T segment and, less frequently, prolongation of the P–R interval (Giraud-Costa and Raybaud[6]). These have been described in 25 to 70% of the cases examined, the difference in prevalence apparently depending on the frequence and the period during which electrocardiographic records were taken. It was stressed that the electrocardiographic changes appear either during the febrile stage or after defervescence. As stated by Giraud-Costa and Raybaud[6] "the patients come to the hospital and leave it with normal electrocardiograms." In most cases the changes are transitory and rarely last more than 3 weeks.

Clinical and pathological evidence of pericarditis is practically never found in typhoid fever. Electrocardiographic changes of pericarditis are apparently extremely rare and hardly mentioned in the literature available. Stuart and Pullen[12] mentioned that in one out of the 16 cases examined by them the electrocardiogram showed changes compatible with pericarditis. Mainzer[8] mentioned the occurrence of displacement of the S–T segment "below or above the isoelectric line" in enteric fever. The electrocardiogram of our first patient showed changes pathognomonic of pericarditis. In this case, unlike cases which show myocardial involvement alone (Rachmilewitz and Braun[10]), the electrocardiographic alterations were not influenced by niacin. In the other 2 patients the signs of pericarditis were preceded by alterations indicative of myocardial involvement. This suggests that we are dealing with myocardial damage in various layers of the heart muscle at various stages of the disease, a possibility which is in keeping with the concept that the electrocardiographic changes of pericarditis are actually due to subepicardial myocarditis (Levine[7]).

Summary. Electrocardiographic signs of pericarditis were observed in 3 patients with typhoid fever. In 2 of the cases the changes were preceded by electrocardiographic evidence of myocardial involvement, usually found in typhoid fever. In one case the changes were characteristic of "pure" pericardial involvement. The changes of pericarditis were observed during a relapse in one case, and during the second or third week of the disease in the other 2 cases. In all cases they appeared after defervescence, and in 2 cases lasted 4 to 5 days; in one case they lasted more than 2 weeks. No clinical or roentgenographic evidence of pericarditis was found and no special treatment was required.

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SUMMARIO IN INTERLINGUA

Signos Electrocardiographic de Pericarditis in Febre Typhoide

Signos electrocardiographic de pericarditis esseva observate in 3 patientes con febre typhoide. In 2 del casos le alterationes esseva precedite per evidentia electrocardiographic de un affection myocardial del typo usualmente trovate in febre typhoide. In un caso le alterationes esseva characteristic de un affection pericardial "pur." Le alterationes de pericarditis esseva observate in recidiva in un del casos e durante le secunde o tertie septimana del curso del morbo in le altere 2. In omne le 3, le alterationes occurreva post defervescentia. In 2 casos illos durava 4 a 5 dies; in un caso illos durava plus que 2 septimanas. Nulle prova clinic o roentgenographic de pericarditis esseva trovate, e nulle special tractamento esseva requirite.

SUMMARIO IN INTERLINGUA

(See page 453 for original article)

Pseudo-Pseudohypoparathyroidismo

Tres membros de un familia—matre, filia, e filio—esseva studiate post que le matre e le filia se habeva presentate al tractamento pro micre dolorose nodulos subcutanee e quando le diagnose de pseudo-pseudohypoparathyroidismo pareva probabile.

Iste patientes esseva de statura compacte. Lor altura esseva minus que 5 pedes. Illes esseva brachydactylic. Determinationes del nivellos de calcium, phosphoro, e phosphatase in le sero produceva valores normal. In 2 del 3 le test de Ellsworth-Howard esseva effectuate, e ben que il esseva necessari injicer le hormon parathyroide per via intramuscular, nulle augmento del phosphaturia esseva notate. A parte le ossificationes subcutanee, anormalitates skeletic esseva notate como per exemplo exostoses e dysplasia coxal. Altere constatationes facite in un o plures del patientes includeva calcification de gangliones basal, diabete mellite, hypothyroidismo, reducite excretion urinari de 17-cetosteroides, e absentia de hormon folliculo-stimulatori in le urina.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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SEXUAL FUNCTIONS AND THE NOSE

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EVER since the first recorded comments of Hippocrates, physicians have for more than two thousand years noted an intimate relationship between sexual processes and the nose. Today, despite their age-long awareness, the precise mechanism linking the two is incompletely understood. In the modern era, Bresgen[1] is generally credited with reporting in 1881 that congestion of the nasal mucosa is likely to occur during menstruation. Shortly thereafter, Mackenzie[10] related nasal epistaxis to menstruation and pregnancy and the nasogenital mechanism to dysmenorrhea, while exploring the phenomenon as a normal physiological process. He found that the tissue covering the middle and inferior turbinates and a portion of the nasal septum is anatomically similar to the erectile tissue of the penis. Moreover, he noted that in healthy women engorgement of the nasal cavernous tissue occurred at the onset of each menstrual cycle, rose to a peak, and then subsided with the cessation of flow. The monthly nasal turgescence was either bilateral, unilateral, or alternated from one side of the nasal cavity to the other. This periodic reaction was slight and asymptomatic in some women, but in others, occlusion of the nasal passageways was associated with sneezing, hypersecretion, and coughing.

Periodic epistaxis frequently accompanies nasal congestion at the time of the menses, and it is not unusual for nosebleed to take place in both sexes at the time of puberty. According to Thomson, epistaxis at puberty is a result of "a reflex action between the pituitary membrane and the genital organ." Occasionally, epistaxis in girls and women seems to replace menstruation, which is coincidentally suppressed. For this reason, the phenomenon has been

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called "vicarious menstruation," a term that has virtually vanished today from medical usage. Engorgement of the nasal mucosa, nasal stuffiness, and sneezing have also been observed to accompany pregnancy, sexual excitement, and coitus. To judge from the medical literature, apparently all sorts of reflex symptoms can be associated with pregnancy, sexual stimulation, and sexual acts, although the precise mechanism linking the nasal nerves to the gonads is still conjectural.

Fliess[6] asserted that hyperemia and swelling occurred over certain sites of the turbinates and the tuberculum of the nasal septum; he called these "genital spots" and claimed that by means of topical intranasal treatment he was able to alleviate some instances of dysmenorrhea. In addition, he also described intense nasal sensitivity and nasal congestion as accompaniments of lactation, which presumably corresponded to the time of menstruation, as well as several cases of abortion which he thought were produced accidentally during intranasal surgical procedures. According to Brettauer[2], dysmenorrhea could be successfully treated by cocainization and cauterization of the nasal mucosa. Endriss[4] listed the nasal symptoms that took place during genital excitation; these included sneezing, nasal obstruction, headache, and altered amounts of nasal secretion which accompanied menstruation, coitus, pregnancy, and onanism. He also described the possibility of olfactory hallucinations ensuing at the menopause, and of anosmia developing after castration procedures and the menopause. Various authors have expressed the belief that the odor of ozena is worse during menstruation and that it is less troublesome with the advent of pregnancy.

Mohun[12] observed a group of 8 patients with vasomotor rhinitis who evinced no nasal complaints when they were not pregnant. One patient had displayed vasomotor rhinitis during 3 previous pregnancies, 2 patients manifesting similar nasal findings during 2 previous pregnancies, and 2 patients showing vasomotor rhinitis complaints during one previous pregnancy. In all instances, the nasal symptoms persisted until termination of the pregnancy, but were either eliminated or greatly reduced in intensity within one week post-partum. At the onset of vasomotor rhinitis, intranasal examination revealed swelling of the erectile tissues and increased redness of the nasal mucosa. As pregnancy progressed, nasal symptoms became more pronounced, and most of the patients manifested increasing tissue swelling and hyperemia, with a few exhibiting edema of the nasal mucosa. In an additional report covering 12 women with hay fever and perennial allergy, the author noted a pronounced intensification of nasal symptoms during pregnancy. Mortimer, Wright and Collip[13a] were able to relieve symptoms of atrophic rhinitis by injecting estrogenic hormone, noting the state of vasomotor rhinitis in the presence of excessive amounts of circulating estrogenic hormone.

According to Holmes, Goodell, Wolf, and Wolff[8], sexual excitement, menstruation, and pregnancy are accompanied by changes in the nasal mucosa, notably hyperemia, hypersecretion, and nasal stuffiness. Alterations in nasal function appeared to depend for their occurrence on individual physiological and emotional responses involving feelings of guilt and humiliation rather than, as maintained by other investigators, on the amount of sex hormones present in the body. When the response to sexual excitement, coitus, menstruation, and pregnancy was sufficiently intense and significantly prolonged, troublesome nasal symptoms followed.

Fabricant[5] found that the topical temperature of the clinically normal nasal mucosa in a married adult male, who engaged in coitus with his wife on six separate occasions over a 5-month period, showed a post-coital rise ranging from 3.5 to 6.5° F. Nasal temperature readings were taken approximately 20 minutes before coitus and repeated within 5 minutes after termination of the sexual act. A rise in the topical temperature of the mucosa of the upper respiratory tract indicates vasodilatation, while a fall in temperature indicates vasoconstriction. Chilling the body surface causes three phenomena: a fall in the topical temperature of the nasal mucosa, a pronounced reflex vasoconstriction, and a diminution of the blood supply. On the basis of the evidence produced in this investigation, it is reasonable to assume that the act of coitus not only produces a rise in the topical temperature of the nasal mucosa but also a state of vasodilatation and an associated increase in the blood supply of the nasal mucosa.

In the domain of animal experimentation, Magnotti[11] extirpated the olfactory bulbs of 8 male and 8 female guinea pigs, destroying visual perception by cauterization of the animals' corneas. Thus surgically treated, sexual desire was eliminated in the animals and no litters ensued. On microscopic examination, it was thought evidence was presented to show the arrested development of testicles, ovaries and tubes. Experimenting with a group of 40 rabbits, guinea pigs and dogs, Karpow[9] claimed that extirpation of the inferior turbinates was followed by failure of descent and loss of weight of the testicles. Weak aqueous extracts of the turbinates taken from a guinea pig caused contraction, with increased tonus, in strips of uterine musculature taken from the same animal. Contraction was greater in pregnant animals and in animals previously pregnant. He believed that he was dealing with a specific uterine-stimulating substance found in turbinates. Nemours[14] repeated some of Karpow's work and obtained similar results.

Hamilton[7] injected testosterone propionate into 15 monkeys and 8 human subjects, provoking nasal congestion, swelling, and narrowing, as well as increased amounts of moisture in specialized nasal areas of the turbinates found in both species. Perivascular congestion was observed in the turbinates of the male and female monkeys. Tebbutt[17] confirmed the work of Hamilton when he found that testosterone acetate and testosterone propionate caused changes in the specialized nasal areas of 12 monkeys similar to those already described. Rosen[16a,b,c] studied the naso-genital relationship in a series of investigations, demonstrating that pseudo-pregnancy could frequently be induced in adult female albino rats following the intranasal application of silver nitrate. This investigation suggested the existence of a naso-genital relationship in which nasal stimulation elicited an ovarian response, a diestrual prolongation. On the basis of luteal ovaries and decidual reactions in traumatized uteri, the prolongation was considered pseudo-pregnancy. He also suggested the possibility of a continuous nerve pathway from the vidian ganglion to the sheath and the substance of the anterior lobe of the pituitary gland. It was implied that the relationship of the nose to the genital organs may be that of nerve stimulation from the nose to the anterior lobe of the pituitary gland and that of hormonal stimulation from that source to the gonads. Shelesnyak and Rosen studied the effects of stimulation and depression of the nasal mucosa on the induction of pseudopregnancy in rats. They found that stimulation with

oleum sinapis appeared to affect the regularity of the estrus cycle, principally in the follicular phase, and that the depressing substances, tannic acid and trichloracetic acid, produced prolongation of the diestrual phase in some of their adult female rats.

Extracting nasal and sinal mucosa from freshly slaughtered cattle, Eggston[3] injected the extract subcutaneously into young female mice for a period of several days, then removing and weighing the uterus, tubes and ovaries. He found that in some mice the weight of these organs doubled that obtained from control animals. Congestion and edema of the tubes and the uterus were detected. The author concluded that nasal and sinal mucosa of cattle contained an estrogenic hormone. Ogihara[15] discussed the changes of the vaginal secretions in female rats in which the nasal mucosa was treated. Applications of saline solution diluted with alcohol to the nose produced a slight, transitory increase of the sexual function; when this application was more prolonged, a depressed sexual function ensued. With moderate stimulations produced by two injections of 70% alcohol, sexual function was first depressed, then increased. A spray of tincture of iodine, or the application of cocaine or 10% silver nitrate solution produced depression of the sexual function. The author concluded that the disturbance of sexual function produced by extirpation of the turbinates could be attributed to the removal of a specific substance contained in the turbinates.

Mortimer, Wright and Collip[13b,c] stated that there is a specific gross and microscopic influence of the mucosal covering of the middle and inferior turbinates of the *Macaca mulatta* monkey in response to the administration of estrogens, as expressed in terms of reddening and swelling of the nasal mucosa, which is associated with the sex changes known to occur in the nipple and the sex areas of the skin of the face and the back. This occurs both in mature and immature males as well as in females. Moreover, it was found that premenstrual exaltations of nasal activity occur in untreated immature and adult female animals and that, for the most part, these peaks are especially pronounced in the autumn, which is the period of greatest fertility. The authors maintained that the hormones of the ovary have a specific physiological nasal effect during the menstrual cycle in the monkey and during the pregnancy of human beings. This is characterized as hyperemia followed by perivascular edema of the submucosa which, if prolonged or excessive, leads to cellular infiltration and prominent enlargement of the turbinates. Mortimer stated that there is a parallel between the increasing hyperemia of the turbinates and the increasing elimination of estrogen in the urine during pregnancy and that these both fall off sharply after delivery.

That there is a relationship between sexual functions and the nose is evident from the foregoing comments. The naso-genital relationship, observed and at the same time relatively neglected for more than two thousand years, is worthy of rescue from the domain of neglect. The entire field of investigation awaits the attention of intrepid investigators.

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DERMATOLOGY AND SYPHILOLOGY

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GYNECODERMATOLOGIC DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE

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CUTANEOUS diseases of the external genitalia are of paramount importance to every physician, especially the gynecologist who in many cases is the first to see the lesions in their early stages and the internist because of associated systemic disease. Although some processes are benign and annoying, others are so serious that early accurate diagnosis may be life saving. In those cutaneous expressions which are not clearly identified morphologically certain basic diagnostic procedures are essential, and foremost among these is an adequate tissue specimen, examined by one competent in dermatopathology.

In general, cutaneous lesions on the genital region show a somewhat modified clinical pattern from similar lesions in other parts of the body, because of the anatomic and physiologic characteristics of the area: loose, intertriginous, hyperpigmented and highly vascular. These conditions predispose to larger and more succulent cutaneous lesions. The intertriginous aspects of the area influences the surface appearance of the lesions (maceration) and increased pigmentation of the locus tends to make most lesions hyperpigmented.

Winer and Winer[54] in 1949 outlined many of the cutaneous disorders of the genital region. We have modified their table to include only those processes found on the female genitalia.

Classification of Genital Skin Lesions

I. Infections
  A. Venereal Infections
    1. Syphilis
      a. Primary
        hard chancre

giant or macro chancre
phagodenic chancre
mixed chancre
edema indurativum
b. Secondary
eroded papules
condylomata lata
c. Tertiary
ulceronodular
gumma
2. Chancroid (ulcus molle or soft chancre)
3. Lymphopathia venereum (Lymphogranuloma inguinale)
4. Granuloma inguinale

B. Non-Venereal Infections
1. Pyodermas
a. Impetigo contagiosa
b. Furunculosis
c. Pyogenic granuloma
2. Tuberculosis
a. Primary complex (tuberculous) chancre of newborn
b. Tuberculosis ulcerosa
c. Tuberculosis colliquativa (scrofuloderma)
3. Fungus and yeasts
a. Trichophytoses
b. Moniliasis
4. Viral and possible viral infections
a. Herpes progenitalis (Herpes simplex)
b. Molluscum contagiosum
c. Ulcus vulvae acutum
d. Verrucae vulgaris
e. Condylomata acuminata
f. Herpes zoster

II. Infestations
A. Scabies
B. Tick, bedbug, flea
C. Pediculosis: both venereal and nonvenereal

III. Inflammatory Dermatoses
A. Papulo-Squamous eruptions
1. Seborrheic dermatitis
2. Psoriasis vulgaris
3. Lichen Planus

B. Contact Dermatitis and Allergies
1. Angioneurotic edema
2. Dermatitis venenata
3. Intertrigo (chafing)
4. Dermatitis medicamentosa (fixed drug eruption)

IV. Atrophies
A. Kraurosis vulvae
B. Lichen sclerosus et atrophicus
C. Roentgen dermatitis

V. Pigment changes
A. Vitiligo
B. Leukoderma
C. Chloasma
D. Tattoo reactions

VI. Neoplasms
A. Benign
1. Angiomas and telangiectases
2. Nevi (moles)
3. Epidermal cysts (steatomas)
B. Precancerous
1. Leukoplakia
2. Bowen's disease (intraepidermal carcinoma)
C. Malignant
1. Squamous cell carcinoma
2. Malignant melanoma

VII. Traumatic
A. Abrasions and lacerations (haircuts)
B. Burns and scalds
C. Traumatic ulcers
D. Decubitus ulcers

VIII. Psychogenic, neurogenic and metabolic
A. Pruritus, neurogenic (brain injuries, diabetes)
B. Neurodermatitis
C. Chronic exudative dermatitis (Sulzberger-Garbe)

Most of these diseases need no special elaboration, but three of them, pruritus vulvae, the white lesions of the external genitalia and tumors deserve particular emphasis. These processes are of interest to the internist largely because

of their potential systemic relationships. A fourth group of diseases of the skin related to gynecology (the dermatoses of pregnancy) has already been discussed[41]. There is considerable overlap in the discussion of pruritus vulvae and leukoplakia since the latter is one of the causes or predisposing factors to vulvar itching.

Another interesting but rare entity occurs in areas of the body where apocrine glands are present and therefore involves the vulvar skin. This process, known as Fox-Fordyce disease, is extremely pruritic and is characterized by closely set, dome shaped, minute papules, flesh to pink in color. These papules seem to be follicular in origin. The cause of this disorder is unknown and in general it is resistant to treatment[16].

PRURITUS VULVAE. Itching of the vulva is a common distressing problem. Pruritus vulvae is a symptom and not a disease and diagnostic effort and treatment must be directed toward the disease which causes the pruritus. Although many cases of vulvar pruritus are of neurodermatitic origin any minor source of irritation may result in prolonged paroxysms of itching. The more the patient scratches, the more the local trauma, the more severe the itch. Thus results an exceedingly complex vicious cycle. The more classical dermatological entities such as lichen planus, seborrheic dermatitis, fungous infection or psoriasis offer no serious problem in diagnosis of the background of many cases of vulvar pruritus. Obviously in the proper management of pruritus vulvae a gynecologic examination is mandatory, since it would be foolhardy to treat the cutaneous surface when the causative factor resides in the vagina, cervix or corporus uteri.

In Karnaky's[27] study covering 20 years of gynecologic practice, 97% of pruritus vulvae was found to be due to trichomonas vaginalis or monilia albicans. Pastras, Beerman and Jumbala[41] also noted that trichomonas vaginalis and moniliasis were the most common causes of pruritus vulvae during pregnancy. Mussey[34] states that most prominent among the reasons for vulvar itching is infection with *Candida albicans*. Ruch[47] found 84% of his cases due to neurodermatitis. It would therefore appear worthwhile in dealing with the problem of pruritus vulvae to be able to exclude these causes as soon as possible. Among other causes of pruritus vulvae, superficial fungous infection should be considered. Microscopic examination of scales or vesicle tops in 10 to 20% sodium or potassium hydroxide as well as by culture on Sabouraud's medium will easily establish the presence of fungi. Parasitic infestation, often overlooked, should be kept in mind, especially pediculosis pubis. This disorder is characterized by the presence of nits stuck to the hair shafts or the living adult lice on the skin surface. In addition, one may occasionally observe maculae cerulae. These small gray macules occur on the chest, abdomen or proximal portion of the extremities. Pinworms are usually found in children although some cases are encountered among adults. Anything capable of causing inflammation and producing even a mild vaginal leukorrhea may be responsible for pruritus vulvae. This then would include physiological, mechanical, chemical or bacterial causes. It can be seen that the specific agents responsible for pruritus vulvae are multitudinous and in the problem cases require special attention to details.

Osborne and Stoll[39] in a study based on the literature over 25 years as well as the records of 500 cases of pruritus ani et vulvae classify the cause of this disease as: local primary irritation; contact dermatitis; specific dermato-

logical disease; anal, rectal, and genitourinary diseases; disease of other organs, and psychogenic disturbances. They believe that the local primary irritation group is by far largest, and indicate that three most common sources of irritation are: 1) leukorrhea 2) daily use of toilet soap and 3) the retention of fecal remnants in folds of the anal skin. Contact dermatitis is the second most common cause of itching in the anogenital region. The principal allergenic substances include local medication, toilet paper, suppositories, enema and douche nozzles, resin finishes on fabrics, drugs taken by mouth, nail lacquer, deodorants, plant oleoresins, contraceptives, and some foods. The clinical features of an anogenital pruritus due to specific sensitization are easily recognized. The pruritus begins around the anus and thereafter itching of the vulva and surrounding areas develops. Depending on the severity the entire area becomes confluent and the dermatitis may spread to involve the thighs and crural folds. In some cases the severity of the dermatitis fluctuates directly with the frequency of ingestion of the offending agent. Contact dermatitis of the vulva without associated involvement of the anal area, although infrequent, does occur. In this type substances commonly found to be causative include local medication, suppositories, contraceptives, sanitary pads, tampons, douche nozzles, pessaries, nail lacquer, plant oleoresins, and certain drugs excreted through the urine. Occasionally unilateral contact dermatitis is due to specific hypersensitivity to nail lacquer and is found on the left side due to contact with the fingernails of the right hand. Specific dermatological entities include dermatitis medicamentosa, psoriasis, seborrheic dermatitis, neurodermatitis, fungal infection, intertrigo, miliaria, lichen sclerosus et atrophicus, parasitic infestation, collagen diseases and many others. Obviously in order to identify many of these diseases one must have special dermatologic training and experience. In addition many cases require histologic confirmation, and other special laboratory examinations. Anal itching resulting from anorectal disorders does occur. The following anorectal disorders are the most common causes of such itching: cryptitis, hemorrhoiditis, fissures, sinuses, fistulas, proctitis, neoplasm, and polyps. Therefore it is mandatory that the clinician perform a thorough proctological examination in persistent cases of anal pruritus. Osborne and Stoll[39] consider urticaria the most common generalized disease which results in pruritus ani. The patients develop itching in the anogenital area with extreme ease, but examination of the entire integument will reveal evidence of urticaria elsewhere. Many systemic diseases are mentioned in the literature as a cause of anogenital pruritus. Among these are: endocrine diseases, neurological disturbances, hepatic disease, prostatitis, cystitis, appendicitis, intestinal parasites, bladder stone, vesiculitis, uterine diseases, lymphoma and others. These must be eliminated as factors before incriminating a local cause. Contrary to the opinion expressed in three popular dermatological texts where emphasis is given to psychogenic factors as the major cause[3,38,42], Osborne and Stoll[39] agree that psychogenic disturbances aggravate an existing anogenital pruritus, but do not feel that they are primary etiological agents. They urge that more time be spent in searching for an underlying organic cause for the anogenital pruritus rather than attributing this disorder to emotional disturbances. Osborne and Stoll[39] summarize this difficult problem:

"The treatment of anogenital pruritus depends on the determination of the cause of the pruritus. More attention must be given to a search for primary irritants, such as the use of soap, leukorrhea, retained fecal matter, and local medications. Contact dermatitis due to specific hypersensitivity is a distinctive entity and its cause must be determined. Oleoresins in condiments should not be overlooked. Specific dermatological diseases of the anogenital area must be correctly diagnosed and treatment based thereon. The gynecologist and proctologist need consultation with the dermatologist and certainly the reverse holds true. Anogenital pruritus in some cases may be but a symptom of an internal medical condition. Psychogenic disturbances and emotional stress are always a factor in anogenital pruritus, but they should never be assigned the primary etiological role without complete examination and consideration of all other possible causes."

Hill[23] believes that in 75% of the cases of pruritus vulvae a neurogenic or functional factor is the probable cause and that lichen sclerosus et atrophicus, kraurosis with or without leukoplakia, and senile pruritus account for about 15%. The remaining 10% are due to diabetes, infections with trichomonas or fungi, and allergy to food and drugs. Clinical diagnosis based on symptoms is not as reliable as diagnosis based on signs. The most frequent local change in cases of vulvar pruritus is an eczematous reaction. This reaction is caused by all diseases except lichen sclerosus et atrophicus, kraurosis with or without leukoplakia, and senile changes. When eczematoid changes are maximal, the white, soggy, thickened skin is confused with leukoplakia.

Pruritus Vulvae in Post Menopausal Women. Parker, Jones and Carter[40] claim that pruritus vulvae in postclimacteric women poses a special problem. The cause of the itching is related to the altered physiology of the area as well as to estrogen depletion. Following or concurrent with the estrogen decrease there is atrophy of the skin and mucosa of the vulva with loss of the subcutaneous fat and thinning of the hair. In the corium there is a notable decrease in the vascularity and an increase in fibrous tissue. Due to the decrease in the number of epithelial cells the glycogen content decreases. This, in turn, promotes a mixed vaginal flora rather than a flora of lactic acid-producing Döderlein bacilli. The final result is that the vaginal reaction becomes pH of 6 to 7 instead of the normal range of 3.5 to 4.5. The total of these physiological changes increases the vulnerability of the vagina and vulva to bacterial, chemical and mechanical irritation. It is interesting that because of these physiological changes the frequency of mycotic vulvar vaginitis decreases tremendously. Parker, Jones and Carter[40] emphasize that in the absence of diabetes mellitus or prolonged antibiotic therapy mycotic vulvovaginitis is rarely seen in this age group. At this point it is worth emphasizing that patients who have had prolonged, continuous, or repeated oral courses of certain antibiotics will often develop fungal infections in the vaginal, vulvar or perianal regions. This develops more frequently when local or intravaginal antibiotic medications are used. Therefore in view of the extensive use of antibiotics today these must be considered in the history of any patient with pruritus vulvae. Parker, Jones and Carter[40] list as the local or specific genital tract causes of pruritus vulvae in this age group as: senile vulvovaginitis, trichomonas vulvovaginitis, atrophic and hypertrophic vulvitis, leukoplakic vulvitis and carcinoma of the vulva. The psychogenic component in pruritus vulvae should not be overlooked. Although primary neurodermatitis is unusual in this age group, it must still be considered as one of the causative factors. In addition, secondary psychosomatic

factors are always present and tend to perpetuate the pruritus, regardless of the cause.

Senile vulvovaginitis is the most frequent cause of pruritus in the postmenopausal age group. Although itching and burning are prominent symptoms there is little or no discharge. On examination there is atrophy of the vulva and vaginal mucosa. In addition there are localized areas of submucosal hemorrhage. The diagnosis is confirmed by the absence of any specific infective agent and of hypertrophic or leukoplakic areas. The problem in senile vulvovaginitis is one of local estrogenic deficiency and is best treated by the local application of estrogenic vaginal cream. Systemic use of estrogens is not needed, since in contrast to their local use, these drugs when administered may lead to estrogenic withdrawal bleeding.

While Parker, Jones and Carter[40] believe that trichomoniasis is the major cause of pruritus vulvae in the childbearing period, they feel that it occasionally produces mild symptoms in the post-climacteric patient. In such cases one notes a frothy greenish-yellow discharge associated with a scanty amount of mucus, edema and hyperemia of the vulva, vagina and cervix. The posterior vaginal fornix shows a strawberry-like granular hemorrhagic stippling. Diagnosis is easily confirmed by direct microscopic examination of the vaginal secretions. Because of the atrophic vaginal and vulvar tissue in elderly patients mild acid douches or acid jellies should be used in preference to other chemical medicaments to control trichomoniasis.

Atrophic and hypertrophic vulvitis is rare in women during the menstruating age, but is relately common in the postclimacteric patient. Atrophy is the result of estrogenic deficiency while local hypertrophic changes are the result of secondary factors such as trauma, uncleanliness and prolapsus uteri. Pruritus is the dominant and most important symptom. The vulvar tissues are atrophic and there may be some areas of hypertrophy. Erosions, fissures, and ulcers are common. Papanicolaou's cytologic and biopsy study are the only reliable means of confirming this diagnosis. In general, with therapy this process is more reversible than leukoplakia. The most important therapeutic procedure is general care and protection given to the vulvar tissues. In addition, estrogenic vaginal cream has some value.

Parker, Jones and Carter[40] state that the cause of leukoplakic vulvitis is unknown, its clinical course is obscure, the histologic picture is controversial and satisfactory treatment is wanting. Leukoplakic vulvitis is most likely to occur after the menopause, but may develop in the childbearing period even in pregnant women. Pruritus produced by leukoplakic vulvitis is most intractable. The vulvar skin is atrophic and blanched in some areas and thickened in others. Erosion, ulceration, and fissuring is common. The diagnosis is confirmed by Papanicolaou's cytologic study and by histological examination of tissue from multiple sites. All raised thickened, infiltrated, ulcerated areas should be studied especially microscopically for invasive malignancy. Over half the patients with carcinoma of the vulva had preceding leukoplakia. Simple vulvectomy is advocated by many authorities for leukoplakia vulvae. However, recurrence of leukoplakia in the transplanted skin varies from 25 to 50%. Because of this recurrence and the postoperative scarring, vulvectomy is not justifiable in all cases. Parker, Jones and Carter[40] advocate simple vulvectomy in those patients who do not respond to all other forms of therapy and who show a pro-

gression of the disease process. In other patients, after a malignant process has been ruled out, conservative therapy with frequent follow-up examinations is recommended. This empirical therapy results in a surprising amount of improvement.

Carcinoma of the vulva is considered the fourth most common genital tract malignancy by Parker and his coworkers[40]. It begins insidiously and therefore is rarely diagnosed early. The patient complains of burning and itching and develops a slow growing lesion in the genital area. The early lesions are not diagnostic clinically and therefore it is mandatory that all indurated or ulcerated areas be excised and examined microscopically. The labia minora, clitoris and vestibule are the most common sites for such cancer although Bartholin gland involvement should not be overlooked. Parker, Jones and Carter[40] indicate that the treatment for carcinoma of the vulva should be radical vulvectomy with bilateral radical groin dissection and extraperitonial pelvic lymphadenectomy.

Greenblatt, Manautou, Griffin and Henry[21] agree that menopausal pruritus vulvae, senile vaginitis and kraurosis vulvae have been associated with estrogen deficiency states. It is recommended that in the treatment of senile vaginitis, estrogens applied locally in the form of suppositories or ointments often relieve the pruritus and improve the senile vaginal changes but cause maturation of the vaginal mucosa[20]. Since 1950 many nonspecific therapeutic medicaments have been tried successfully. Among them are the corticosteroids, especially hydrocortisone. Noojin[35] reported that hydrocortisone was the most successful antipruritic preparation available for topical use, stating that hydrocortisone and related compounds consistently relieved intractable pruritus in 4 of 5 patients. Estrogen cream containing hydrocortisone has proved of value as has also the combination of estrogen and an antihistamine preparation in an emollient base. The oral use of an antihistamine drug with a corticoid is extremely effective and will within a few minutes relieve the pruritus of kraurosis vulvae for several hours. In a clinical study of the local treatment for pruritus vulvae by Greenblatt, Manautou, Griffin and Henry[21] an acid emollient base containing estrogen, vitamin A, an antihistaminic and hydrocortisone, singly and in various combinations was used. It was found that the combination containing all four medications was far superior therapeutically in the treatment of pruritus vulvae, regardless of the cause. It was stressed that this local form of therapy is not specific and that the underlying cause for the pruritus when it can be identified must be treated specifically. Vulvectomy and radical surgery are still the treatment of choice for leukoplakia of the vulva, but in cases of kraurosis vulvae, if the pruritus is alleviated and the patient watched closely, surgery may often be avoided. It is felt that it is not the kraurosis but the trauma, irritation, infection and reinfection which predispose to the development of leukoplakia of the vulva and malignancy.

Reich and Nechtow[46] treated 228 cases of intractable pruritus vulvae during a period of approximately 10 years. In order for any case to be considered cured, the pruritus had to be controlled for a minimum of one year. In general these patients complained of severe itching of the vulva and study by Papanicolaou smears, biopsies and cultures eliminated any specific causes for the pruritus. Because of the lack of demonstrable organic causes this type of pruritus vulvae was labeled as intractable. The duration of the pruritus varied from 6 months to 22 years;

(average 5 years). The patients ages ranged from 28 to 72 years; (average 45 years). The procedure for the injection therapy consists in preliminary cleansing of the vulva and surrounding area with soap and water. The pubic hair is not shaved. With the use of 1% procaine solution and a 27 gauge hypodermic needle procaine wheals are made at the site of the entrance of a spinal needle. Through these wheals an additional 2 to 3 ml. of procaine is injected into the subcutaneous parts of the labia on both sides. Finally with the use of a large spinal needle a zylcaine oil mixture is injected into the labia. In general from 5 to 10 ml. is required for each labium. It is important that the quantity of the oil mixture delivered be just short of producing tenseness of the overlying skin, otherwise the complication of sloughing may occur. In this series delayed "cures" were encountered in some patients: the longest time being 2½ months. Reich and Nechtow[46] state that this form of therapy was effective in a large but unspecified percentage of the cases. They also state that they do not know why this treatment is effective, but it may be due to breaking of the pain cycle or possibly the reaction of the tissues to the oil acting as a foreign body results in microscopic fibrosis of the fine nerve elements.

Finkler[18] investigated the effectiveness of locally applied hydrocortisone in the treatment of vulvar and vaginal pruritus on forty (40) consecutive private office patients of various age groups. The medication was used mainly for the symptomatic relief of the pruritus, the causative agent was ignored. In general the primary diagnoses were varied. Vaginal tablets containing 10 mg. of hydrocortisone free alcohol in carbowax base were prescribed with instructions to insert one tablet deep in the vagina daily. In the more severe cases one tablet twice daily was prescribed for the first 2 or 3 days. The overall results were excellent, in 77% of the patients the pruritus was eliminated while an additional 7% experienced some degree of relief. There were no undesirable effects of the hydrocortisone, no evidence of systemic absorption, nor local irritation from the hydrocortisone or its vehicle. In general, relief of the pruritus occurred within the first 24 hours and was effective in all age groups.

WHITE LESIONS OF THE VULVA. In general the literature on the white lesions of the vulva is difficult to assess. Many authors discuss similar diseases under dissimilar names. Hyman and Falk[25] realizing this problem identified and defined their terminology and presented the results of their observations. They list as white lesions of the vulva: lichen simplex chronicus, leukoplakia, Bowen's disease, kraurosis vulvae, lichen sclerosus et atrophicus, and senile and essential atrophy of the vulva. Lichenification (lichen simplex chronicus) results from scratching and is always associated with itching. Primarily lichenification is a disease of the skin which may occasionally spread to the mucocutaneous tissues. When the genital mucocutaneous tissues are involved, lichenification can mimic leukoplakia, and to make diagnosis even more difficult these two conditions are commonly found together. Lichenification leads to thickening of the skin with increased cutaneous markings, the thickening is in the form of plaques the outlines of which are not sharply marginated. This is in contrast to the plaques of true leukoplakic areas which are sharply outlined. In addition the plaques of lichen simplex chronicus (lichenification) are not pure white but rather erythematous or hyperpigmented. Lichenification is found in all age groups but is more frequent in the

adult and especially postmenopausal women. Leukoplakia is primarily a disease of the mucosa or mucocutaneous tissue, but in advanced cases may spread onto the true skin.

Trauma of scratching often produces erosive changes in leukoplakic areas as well as in lichenified areas. Erosive changes associated with lichenification do not predispose to malignant change, whereas erosions, ulcers, or even keratoses in leukoplakia are warning signals that malignancy has occurred and certainly warrant histological examination. In general leukoplakia is limited to the adult age groups. Bowen's disease presents itself as a rough thick white plaque. This lesion is pruritic, spreads slowly and sometimes develops erosions and ulcers. The rough verrucous surface should suggest that more than lichenification is present. Bowen's disease involves the skin as well as the mucocutaneous tissue and is most common in the late adult age groups.

Lichen sclerosus et atrophicus of the vulva involves the skin as well as the mucocutaneous tissues. The size of the labia and introitus may be normal or contracted. The periphery of the involved areas is well defined and telltale satellite flat-topped atrophic papules may be seen. In general the tissue covering the vulva is thinned. The surface of the involved sites will often show the characteristic cigarette-paper wrinkling. The perianal and perineal skin is often affected at the same time and in a similar manner. The primary lesions of lichen sclerosus et atrophicus may be found on many other areas, especially around the anus, sides of the neck around the umbilicus and submammary folds. The patient may have complaints referable to the genitalia because of friability of the tissue and tightening of the introitus. In the early stages the color of the vulva may be bright crimson, although in general when seen the color of the vulva is usually white. Occasionally in children lichen sclerosus et atrophicus of the vulvar area may completely resolve. Since pruritus is a common accompaniment of lichen sclerosus et atrophicus, it would not be surprising to find areas of lichenification adjacent to the lesions of lichen sclerosus et atrophicus. In addition, leukoplakic areas may develop next to areas of lichen sclerosus et atrophicus, and in all probability are responsible for those cases of malignancy reported to have developed from lichen sclerosus et atrophicus.

In ordinary uncomplicated senile changes of the vulva there is no pruritus, the labia simply shrink and become absorbed. Usually in this group there are no other symptoms.

As far as kraurosis vulvae is concerned, Hyman and Falk[25] limit this diagnosis to the rare combination of narrowing and tightening of the introitus associated with disappearance of the labia, but without thinning of the skin. This combination although rare may be found in all age groups. These patients usually suffer with dyspareunia. According to Hyman and Falk[25] essential tightening of the introitus would be a good descriptive term for this condition.

It is important that it be noted that Hyman and Falk[25] condemn vulvectomy as the treatment for lichen simplex chronicus, lichen sclerosus et atrophicus, senile vulvar atrophy and essential narrowing of the introitus. They stress that vulvectomy should be performed in leukoplakia only if there is evidence of malignancy or impending malignancy. They recommend the procedure for Bowen's disease and Paget's disease.

Based on a study of 100 cases of vulvar leukoplakia and kraurosis, Wallace and Whimster[52] had earlier pointed out the confusion in terminol-

ogy and the lack of coordination between the dermatologist and gynecologist in investigating vulvar atrophy and leukoplakia. They recognized 1) primary atrophy and sclerosis of the vulva, corresponding to Darier's kraurosis, 2) leukoplakia vulvae which may arise independently or may be a complication of primary atrophy or of 3) lichen sclerosus which affects other parts of the body apart from the vulva and perineum 4) senile genital atrophy. They found leukoplakia in 6 of 15 patients suffering from primary atrophy though cases have been observed up to 10 years without this complication. In 21 patients leukoplakia was seen without other complication. This may or may not be associated with shrinkage or atrophy of the affected parts and in 2 patients was associated with leukoplakia of the tongue. Pruritus is the main symptom and malignant change is likely to occur. The signs and symptoms in all of these diseases is variable and it is doubtful whether endocrine, vitamin or other measures affect their course. The causes are entirely obscure.

Likewise Halter[22] indicates that leukoplakia and kraurosis represent the most frequent precancerous changes of the vulva. Among 40 personal cases of carcinoma of the vulva were 14 extensive leukoplakia and 4 kraurosis. Conservative treatment is given for small lesions. Six out of 8 cases of kraurosis were cured by hormonal treatment alone. In leukoplakia and carcinoma he recommends electrocoagulation. Recurrences are relatively infrequent.

Leukoplakia of the Vulva. Leukoplakia of the vulva mentioned previously in connection with pruritus vulvae clinically presents patchy, grayish white infiltrated plaques. Fissuring and edema are often associated. Irritation, soreness and pruritus are common symptoms. Leukoplakia of the vulva is most frequently seen in elderly women, and is uncommon in the Negro race. Although most vulvar carcinomas appear to develop on a leukoplakic background, it has never been convincingly demonstrated that most leukoplakias of the vulva terminate in cancer. Miller, Riley, and Stanley[32] reviewed the reported causes for leukoplakia such as the estrogen deficiency concept, the allergic concept, functional factors, vitamin A deficiency theory, and vitamin C deficiency theory. They conclude that neither the cause nor the cure for this disease is as yet known. Although they recognize that surgical excision of the affected skin is commonly carried out, many times with permanent relief, they do not accept this as an entirely satisfactory remedy for the following reasons:

1. "It does not always result in a cure. Recurrence in surgically-treated women is by no means uncommon. 2. For some women vulvectomy may be a somewhat mutilating procedure, leading to additional problems, such as dyspareunia for an already troubled individual. 3. Since the writers' interest in leukoplakia is twofold, namely, a desire to help the patient and, also, a wish to determine the cause, course, and cure, surgical excision has, for them, remained a last resort. However, until the cause and cure of this disease are available, surgery will play a role in its management, especially in older women with intractable pruritus or with evidence of carcinomatous change. In the latter instance, surgery should be radical in character."

Along the same lines Falk and Hyman[16] object to wholesale vulvectomies for the mere presence of leukoplakia. They feel that the supervention of malignancy is probably not more than 15%. They insist on regular careful medical observation with frequent biopsies. In view of leukoplakia being a disease of as yet unknown cause, Miller, Riley, and Stanley[32] assumed that possibly some chronic irritative factor must play a significant role in its causation. They then assumed that some constituent

in the urine may be the substance. With this in mind, the authors have subjected the urine of patients with leukoplakia and those without leukoplakia to careful chemical analysis. It is interesting to note that in leukoplakic patients the urinary excretion rate of organic acids was statistically and significantly higher than for the control group. They plan to investigate the individual urinary organic acids in the near future.

Lichen Sclerosus et Atrophicus in Relation to the Diagnosis "Leukoplakia" and "Kraurosis" of the Vulva. Stahle and Pound[50] warn that the word leukoplakia has different meanings to different physicians. In its strictest sense the term leukoplakia means a white plate or plaque. This appearance may be produced by a variety or dermatological conditions such as lichen planus, lichen sclerosus et atrophicus, fungal infections, psoriasis, eczema and others. Some physicians use the term leukoplakia in its literal sense and not as a diagnosis. Once a definite diagnosis has been made, the disorder is then treated. Therefore used in this way the term leads to no confusion.

In contrast with this, to many physicians the term leukoplakia signifies the name of a disease characterized histologically by epithelial hyperplasia with an underlying cellular reaction. To them this process is considered a common precursor of neoplastic change. The danger of this term being used in these two distinct senses is obvious. It would also seem reasonable to confirm the diagnosis histologically at least before employing any type of definitive therapy.

The term kraurosis refers to dryness, but is also used to indicate shrinkage or narrowing of the vulval parts, including the introitus. Therefore when used in this sense, the term kraurosis can be applied to a variety of conditions. Atrophy of the vulval parts occur in most women around the time of the menopause. The extent of the atrophy varies widely. Dryness is characteristic and is associated with changes in the underlying glands. This atrophy is regarded as physiological atrophy secondary to endocrine changes. Pruritus is commonly associated with this type of atrophy.

Many types of secondary changes result from the trauma of scratching, namely, excoriations, infections and lichenification. Therefore the clinical picture will depend on the type and amount of complications superimposed on the initial atrophy. This picture is seen so commonly that many physicians have been influenced to use the term kraurosis to cover the entire picture of atrophy and its associated complications, and because of the clinical picture others have used the terms leukoplakia and leukoplakic vulvitis loosely to cover the same series of changes. Therefore the term kraurosis would be better discarded or if retained should be used to describe vulval atrophy in its widest sense.

The same problem applies to lichen sclerosus et atrophicus which is often diagnosed as leukoplakia, leukoplakic vulvitis or kraurosis. Stahle and Pound[50] feel that the factors which produce lichen sclerosus et atrophicus of the vulva augment the natural tendency to atrophy, or that vulval tissues possessing the propensity to physiological atrophy are more prone to develop lichen sclerosus et atrophicus in response to the appropriate stimulating factors. Laymon[28] also recognized that confusion existed concerning the relationship of lichen sclerosus et atrophicus to balanitis xerotica obliterans, kraurosis penis and vulvae, atrophic lichen planus, and guttate morphea. He concluded that:

"1. Lichen sclerosus et atrophicus is not related to the atrophic form of lichen planus.

2. Balanitis xerotica obliterans and kraurosis penis are terms which have been applied to the same disease. 3. Balanitis xerotica obliterans (kraurosis penis) represents a form of lichen sclerosus et atrophicus involving the genitals. 4. Lichen sclerosus et atrophicus may occur on the male genitals as (1) isolated papules on the shaft or (2) sclerotic preputial and urethral involvement with patches on the glans. 5. Both types of genital involvement may occur alone or with lesions on the body, and all forms present the same histologic features. 6. There is more evidence favoring the classification of kraurosis vulvae with lichen sclerosus et atrophicus than for regarding it as a distinct entity, since the clinical and histological features seem practically indistinguishable. 7. Because of distinct clinical and histologic differences, it is impossible to say that forms of circumscribed scleroderma and lichen sclerosus are the same. However, because characteristic clinical and histologic lesions of both disorders have occurred in the same patient they probably are closely related to each other."

Schoch and McCuistion[48] also discussed the confusion existing in terminology, concepts and principles of diagnosis and treatment of certain dermatoses of the vulva. The notable examples are the precancerous dermatoses. The basic condition, kraurosis, is a primary sclerosing atrophy and is the same as lichen sclerosus et atrophicus. Leukoplakia is the only true precancerous lesion of those discussed, (*i.e.* kraurosis, lichen sclerosus et atrophicus, lichen planus, senile atrophy, scleroderma, and leukoplakia).

Clark[11] made an attempt to define and clarify in histologic terms some of the problems associated with kraurosis, lichen sclerosus et atrophicus, and leukoplakia of the vulva. One hundred forty seven biopsies or surgical specimens of the vulva from 117 patients were studied. In the group diagnosed kraurosis vulvae, 14 (12.6%) patients presented histological changes basically identical to those seen in lichen sclerosus et atrophicus. A histological diagnosis of leukoplakia was made in only 2 of 111 patients (1.8%) so diagnosed clinically.

The microscopic features of kraurosis vulvae (lichen sclerosus et atrophicus) are distinctive enough so that the diagnosis may be made on histological grounds alone. Leukoplakia, on the other hand, is not so easily defined. The microscopic findings of hyperkeratosis and irregular epidermal hyperplasia with a chronic infiltrate in the upper part of the corium is not diagnostic of leukoplakia since similar epidermal changes may be secondary to a variety of inflammatory lesions of the vulva. Clark[11] believes that:

"1. The clinical picture of kraurosis vulvae as described by Darier is usually associated with histological changes identical to those seen in lichen sclerosus et atrophicus. 2. Kraurosis vulvae and lichen sclerosus et atrophicus are virtually identical disorders, histologically; however, in some cases the changes may be confined to the vulva while in others there may be extension to the perianal or extragenital skin. 3. If there is no microscopic hyperplasia of the epidermis in kraurosis vulvae, it should not be considered as premalignant. 4. Lesions diagnosed clinically as leukoplakia do not present a constant, distinctive and diagnostic histological picture. The combination of clinical and histological features which permit the diagnosis of leukoplakia have been presented. 5. Leukoplakia probably does have some histogenetic relationship to epidermoid carcinoma of the vulva, but the importance of leukoplakia of the vulva as a premalignant lesion may have been exaggerated."

Chernosky, Derbes, and Burks[9] report on 39 cases of lichen sclerosus et atrophicus in children. In these 39 cases the age of onset was 13 years or under, with one case beginning at the age of one year. The entire group consisted of female patients. In general the anogenital region is chiefly affected. The neck, upper extremities and upper part of the trunk may also be involved. Of 37 children with lichen sclerosus et atrophicus, 15 (41%) had lesions both inside and outside the anogenital re-

gion, whereas in 9 (24%) only the skin outside the anogenital region was involved.

The best subjective and objective improvement in this disease has resulted from the topical use of hydrocortisone or related compounds. Certainly, surgical procedures such as local excision and vulvectomy are contraindicated even more in children than in adults. A few cases have been reported in which the lesions of lichen sclerosus et atrophicus disappeared spontaneously. This is not surprising, since the course of lichen sclerosus et atrophicus is chronic and unpredictable. The prognosis therefore can not be anticipated.

This survey of some recent opinion indicates how difficult it is to place in proper perspective certain aspects of the problems involved in the white diseases of the vulva, especially kraurosis vulvae and lichen sclerosus et atrophicus. This is especially so if one considers the histopathologic findings in these processes. Clark[11], in his histopathologic study of kraurosis vulvae, lichen sclerosus et atrophicus, and leukoplakia of the vulva, which purports to be a fresh review of a stubborn problem, states the gist of this whole situation, as follows:

"A flat, white lesion on an atrophic vulva may be called kraurosis vulvae by one clinician, leukoplakia by another and atrophic vulvitis by a third. A biopsy taken of this lesion might be diagnosed as kraurosis vulvae by one pathologist, leukoplakia by another, or chronic vulvitis with atrophy by a third. This situation, which is not exaggerated, is not due to incompetence or ignorance but to poor definition of terms and inadequate correlation of clinical and histological findings. There are about as many clinical and histological descriptions of kraurosis vulvae and leukoplakia as there are authors on the subject. One can readily find kraurosis vulvae classified as a 'simple atrophy and shrinkage'[36] or as precancerous disorder[2]. In addition, kraurosis has been described as being identical with lichen sclerosus et atrophicus[28], a lesion familiar to the dermatologist, but virtually hidden from others because of its remarkable name. One may be further confused by Ormsby and Montgomery[38] who state that the histological features in lichen sclerosus et atrophicus and kraurosis vulvae are similar, but the former extends beyond the vulva, while the latter is confined to the mucosal surfaces of the vulva. Stahle and Pound[50] suggest that the terms kraurosis and leukoplakia be discarded; a suggestion that is not without merit."

Clark[11] states further that the ideal solution to the present problem would be to describe and correlate the clinical and histological features of these atrophic and keratotic disorders of the vulva, including kraurosis vulvae, lichen sclerosus et atrophicus, leukoplakia and simple senile atrophy, assigning new names to each clinicopathologic entity. The clinical pictures, however, overlap and the histological features are not entirely distinctive, particularly with regard to leukoplakia. In addition, efforts to revise terminology usually compound confusion and should not be attempted unless on very firm morphologic grounds or, preferably, to present new, accurate etiologic concepts. Here we can only clarify previous morphologic concepts and we have no idea at all about the etiology of these processes. It would seem reasonable, therefore, to use the present clinical terminology and to describe the histological changes usually seen in these clinical states. Hyman and Falk[25] in their study have succeeded in doing this. Although they have not analyzed the literature, some of their conclusions, based on personal correlation of clinical and pathologic aspects are in keeping with the best thought on the subject. Since the histopathologic picture reflects the result of many factors (Roentgen-ray therapy, the phase of the disease present at the time of examination, adequacy of the

specimen, the same histologic pattern for a variety of diseases, and the combination of diseases) there is more need in this group of diseases to correlate the clinical circumstances with the pathologic findings than in some other groups of diseases.

Although there is much evidence to suggest that kraurosis vulvae and lichen sclerosus et atrophicus may be the same disease, one cannot overlook the fact that competent observers have described a variety of phases for kraurosis vulvae. For example Allen states[2] that:

"kraurosis vulvae appears in one or in a combination of the following forms: (1) an initial stage of redness and swelling of the labia; (2) whitish, smooth, glistening atrophic patches with retraction of the skin of the labia and constriction of the vaginal orifice; (3) firm, dry, fissured, ulcerated patches; and (4) keratoses and epidermal carcinomas. Corresponding to the clinical variations, the microscopic picture may show these features combined or singly, commonly in association with a subepidermal infiltration chiefly of mononuclear cells, as in senile keratosis or leukoplakia. It is likely that in many instances the atrophy represents an early stage preceding the formation of the hypertrophic keratoses and finally of the carcinomas. On the other hand, carcinomas may follow directly on the atrophic phase in kraurosis vulvae, a phenomenon reminiscent of the carcinoma developing in atrophic areas of xeroderma pigmentosum, as if epidermal atrophy *per se* embodies a cancerogenic incitant, at least under certain conditions."

If this is a true sequence of events, it is obvious that the time and the course of the disease one takes the specimen conditions the findings. If one takes the specimen at time of atrophy it is understandable that one will find changes exactly duplicating those of lichen sclerosus et atrophicus, whereas at other times the tissue reaction may be that of leukoplakia. These considerations are, however, contingent on the thesis that kraurosis vulvae actually is a specific entity undergoing the evolution described above.

Another conditioning factor in histopathologic differentiation of the vulvar diseases under consideraton is that the specimens contain certain features, for example changes in the deeper vessels, said to be of differential value. Obviously, inadequate specimens are worthless to assess such a difference. It is apparent that one should not grasp at straws for the important differentiation of lichen sclerosus et atrophicus from kraurosis vulvae by the presence or absence of these vascular changes, which are said to be absent in kraurosis vulvae anyway. This same line of argument holds for other differential features, such as the absence of keratinous plugs in kraurosis vulvae and their presence in lichen sclerosus et atrophicus. On the other hand, this brings up a concept in cutaneous pathology namely, since the reactions of the skin are of limited variety, similarity of histologic features need not mean that one is dealing with a similar disease. This is well illustrated by the development of identical epitheliod tubercles in patients with sarcoidosis and in those exhibiting the result of numerous factors in no way related, as far as we presently know, to this disease, for example, silica, beryllium, zirconium, syphilis, tuberculosis, leprosy, and many others.

If one relies on the clinical facts of the case for differentiation, there are other complications. It has been stated that kraurosis vulvae is not associated with cutaneous lesions elsewhere, whereas lichen sclerosus et atrophicus is. Unfortunately for this idea, cases have been seen with only vulvar lesions.

If these diseases are different, how can one tell them apart? Some get around this question by denying that lichen sclerosus et atrophicus can occur in the vulva alone. They claim that

if the patient does have only vulvar lesions, the process is not lichen sclerosus et atrophicus but kraurosis vulvae. Therefore, one must conclude that the difference is largely a matter of definition in which case definition limits thinking. If the definition is too rigid, no exceptions are allowed and no real progress is possible.

Wallace and Whimster[52], in their study of 100 cases of vulval leukoplakia or kraurosis, pointed out that there is not only confusion in terminology, but also lack of coordination between dermatologists and gynecologists in investigating vulval atrophy and leukoplakia. These authorities recognize four processes: (1) Primary atrophy and sclerosis of the vulva (Darier's kraurosis). (2) Leukoplakia vulvae, which may arise independently or may be a complication of primary atrophy; or of (3) Lichen sclerosus et atrophicus which affects other parts of the body besides the vulva and perineum, and (4) Senile genital atrophy. While these are convenient differentiations for individual cases, merely classifying the reactions into any number of groups does not make a clear case for or against identity of these processes. Another compensating factor in the histopathologic differentiation of lichen sclerosus et atrophicus from kraurosis vulvae is that certain cases of kraurosis vulvae (50% according to Allen[2]) develop epidermoid carcinoma. Obviously, cancer may also develop, according to Wallace and Whimster[52], in patients with lichen sclerosus et atrophicus.

On the whole, the balance of evidence is in favor of considering lichen sclerosus et atrophicus and kraurosis vulvae as the same process. While there is some opinion relating scleroderma to lichen sclerosus et atrophicus, there are sufficient differences clinically and histopathologically to stamp them as distinctive diseases. Likewise, lichenification (lichen chronicus simplex) of the vulva is easily differentiated from the other white lesions of this organ.

PAGET'S DISEASE OF THE VULVA. The general problem of extramammary Paget's disease has been discussed previously[4]. Paget's disease of the vulva is a specifically pruritic erythematous, oozing, sharply marginated malignant lesion. Microscopic examination reveals the typical Paget cell. The nature of this clear hydropic cell found in Paget's disease has been the subject of much controversy. Although many authors suggest that the vulval Paget cells originate in the epidermis[15], Lennox and Pearse[29] believe the cells almost certainly arise from the sweat gland. Stout[51] believes that extramammary Paget's disease is usually secondary to carcinoma of the apocrine glands. In general these glands are found in the axilla and anogenital regions, but may be found anywhere on the skin surface as ectopic glands. Although current trend is to regard the cutaneous lesion as secondary spread from an underlying carcinoma[17], the explanation for this process proposed by Pinkus and Gould[43] is pertinent. They suggest that the Paget cell may be regarded as either (1) an autochthonous, altered epidermal cell, changed regressively, that is, degenerated and dyskeratotic, or changed progressively, namely, dedifferentiated and anaplastic: or (2) a cancer cell representing an intraepidermal metastasis from a malignant tumor originating in the mammary gland (modified apocrine gland) or its ducts.

It is generally agreed that Paget's disease occurs in sites other than in the mammary areola and presents in these extramammary lesions a microscopic picture identical with that seen in the breast. There are many cases reported of extramammary Paget's disease of the vulva, some with and some without underlying carcinoma[1,7,14,24,33,

[44,56]. Sonck's[49] patient with Paget's disease of the vulva was a 61-year-old woman who had simultaneous bilateral ovarian carcinoma. She later developed carcinoma of the wall of Douglas' pouch. The carcinoma of the vulva did not seem to be metastatic. Almost all sebaceous glands, hair follicles and ducts were invaded by Paget cells.

It is well known that extramammary Paget's disease also occurs in the human male. In Miescher's[31] case Paget's disease was found on the genitalia, involved the sweat glands and included the development of an infiltrating adenoid carcinoma originating from the surface epithelium. Rabson, Van Scott and Smith[45] observed a 67-year-old white man who had adenocarcinoma of the anorectal junction with features of extramammary Paget's disease. These authors emphasized the value of mucin stains in diagnosis of Paget's disease. Early recognition and eradication of Paget's disease is of utmost importance. This can only be done by an awareness of the disease and immediate study of the lesion microscopically.

Radical vulvectomy without lymph node dissection, and with proper postoperative follow-up[5], is usually the therapy recommended for Paget's disease of the vulva. Woodruff and Hildebrandt[55] point out that although local excision would be adequate in many cases one should understand that these intraepithelial lesions may be of multicentric origin and therefore simple vulvectomy with thorough study of the tissue for evidence of invasive disease is the best form of treatment.

MISCELLANEOUS TUMORS OF THE VULVA. Numerous types of benign and malignant neoplasms may occur on the vulva. The variety of tissues found in this area accounts for a number of types of neoplasms. Adenocarcinomas other than that originating in Bartholin's glands have infrequently been seen. In addition rhabdomyosarcoma and sweat gland tumors may affect the vulva. Danforth[13] reported 6 cases of hidradenoma. He concluded that:

> 1. Hidradenoma is infrequently found in the operating room and laboratory. It is probably far more prevalent than clinical and pathological experience would indicate. 2. The great majority of these growths are benign. 3. Simple excision is quite sufficient for most of them. The exceptional tumor which is, or which becomes, malignant will need more radical attention. 4. The multiple layers of the epithelium of the tumor, which are typical of the gland from which it springs, should not be assumed to be evidence of malignancy. 5. Six cases are reported. Attention is called to the characteristic double layered epithelial lining of the gland from which the tumor arises and which is reproduced in the tumor."

Ober, Palmer and Glassy[37] reviewed and evaluated previously reported cases of sarcoma and described in detail 2 cases of rhabdomyosarcoma one of the vulva and the other of the vagina. Both of these tumors were fungating growth which appeared within a short period of time. Both tumors were relatively superficial both clinically and microscopically. However the cytologic appearance of these tumors was almost the same as rhabdomyosarcomas which disseminate rapidly and widely.

CARCINOMA OF THE VULVA. Although the vulva is rarely a primary source of dissemination, metastatic carcinoma to the skin is a real problem[4]. As would be expected, carcinoma of the breast is a likely source of cutaneous metastases. In general, malignant metastases to the skin are papules, nodules or tumorlike plaques, and in most cases they are located in the vicinity of the primary tumor. Without histological examination of the lesion one ordinarily would not be able even to suggest such a diagnosis. Cianfrani and Smith[10] actually reported a case of diffuse inflammatory cutaneous carcinomatous metastasis secondary to epidermal carcinoma of the vulva.

Primary carcinoma of the vulva is

of more than passing interest to the internist and dermatologist. Since pruritus or leukoplakia[53] may be the earliest expression of the disease, these patients are apt to consult the nonsurgical practitioner rather than the surgeon or gynecologist. In addition to his responsibility for early recognition of vulvar cancer, the internist should have an intelligent understanding of the best therapy as well as the results to be expected from it.

Usually one finds that the patients with vulvar carcinoma are of an advanced age (Callomon and Wilson[6]) (58 years; Watson and Counseller[53]) but it has been observed in very young girls (15 to 18-year-old virgins) (Callomon and Wilson[6]). Carcinoma of the clitoris may afflict women under 40 years (Callomon and Wilson[6]). A solid smooth nodule or a more diffuse palpable infiltration may develop. Since ulceration occurs rapidly, the lesion soon breaks down into a crateriform ulcer or it may result in a papillary growth. Although the course is often rapid, the majority of the vulvar lesions are not unlike those occurring on the skin in other locations of the body[30]. Isaacs and Topek[26] feel that radical surgery is the only means of increasing the 5-year cure rate. Although a one stage procedure including radical node dissection and vulvectomy is ideal, it is suggested that the reported 12% operative mortality may indicate that a two stage or even three stage procedure may be best in poor risk patients. In their patients in whom radical surgical therapy is indicated Watson and Counseller[53] also believe that the two stage procedure appears to reduce morbidity. In general with the older poor-risk patients therapy should be as radical as the patient can tolerate, and when possible the deeper inguinal and femoral lymph nodes should be removed.

In general radiation therapy of squamous cell carcinoma of the vulva is of little benefit (Curtin and Ulfelder[12]). However it is interesting that in some cases Watson and Counseller[53] recommend postoperative radium and Roentgen therapy rather than extensive bilateral dissection of the lymph nodes.

Based on an experience of 238 patients, Green, Ulfelder and Meigs[19] analyzed and reviewed the problems of invasive epidermoid carcinoma of the vulva. Their conclusions form a thorough summary of the treatment situation:

"1. Cancer of the vulva when treated by adequate surgery is far more curable than was formerly realized. In spite of their advanced age and frequently associated obesity, diabetes and cardiovascular disease, surgery of the magnitude necessary to offer optimum chance for cure is tolerated extremely well by these patients."

2. "Leukoplakia is again shown to be an extremely important precursor of malignant change in the vulva, and a prior syphilitic infection also may be of significance in patients in the younger age group, and particularly in Negro women. Certain systemic characteristics which many of these patients have in common also suggest a possible steroid hormone or metabolic disturbance in the etiological background."

3. "With radiation therapy offering little in the management of this disease, surgery is the treatment of choice. The basis for adequate surgery lies in an understanding of the local characteristics of the primary lesion, namely, its diffuseness and multicentric origins, and an appreciation of the frequency and manner of lymphatic spread. Attempts at clinical estimation of the presence or absence of nodal metastasis are highly inaccurate. Certain factors such as type, microscopic grade, size, and location of the primary lesion in-

fluence to some extent the incidence and distribution of lymph node metastases. But when curability is considered, these factors are of considerably less significance compared to whether or not an adequate operation is done. Previous inadequate treatment may complicate the problem but should not alter the basic plan of surgical attack and does not seem to diminish significantly the potential curability."

"4. The ideal operation is a radical vulvectomy with dissection in continuity of the superficial and deep nodes of the groins and pelvis. It has been amply demonstrated that procedures short of this will not yield satisfactory results. Recent use of a lower abdominal crescent incision in combination with a radical vulvectomy exposure has permitted a safe, effective, one-stage, en-bloc resection, and represents a definite technical advance."

"5. More radical pelvic surgery should be considered in dealing with selected patients with large lesions and local extension beyond the vulva, if results in this special group are to improve. If it permits adequate resection of the local disease, posterior pelvic exenteration can apparently be carried out quite safely and with reasonably good chance of cure in these patients."

"6. Last, more aggressive prophylaxis through recognition and proper treatment of the almost universal precursor, leukoplakia, and further efforts to diminish the continuing long delays in diagnosis and treatment will perhaps be of equal importance in improving control of this disease."

Cassidy, Braden and Cerha[8] attempted to correlate the size of primary erosive vulvar lesions with the occurrence of positive lymph node metastasis. They felt that regional lymph node metastasis may be expected in about 14% if the primary lesion is 3 cm. or less in its greatst diameter and in approximately 39% of patients with primary lesions greater than 3 cm.

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BOOK REVIEWS AND NOTICES

IMMUNITY AND VIRUS INFECTIONS. Edited by VICTOR A. NAJJAR, Vanderbilt University School of Medicine. Pp. 262; 54 ills. New York: John Wiley & Sons, Inc., 1959. Price, $10.50.

A BY-PRODUCT of the continuing expansion and acceleration of research is the greater frequency of symposia at which leaders in a limited field of investigation exchange new data and expert opinions. Such a symposium took place in May, 1958, at Vanderbilt, and this book contains the papers that comprised the program. In deference to Sir Macfarlane Burnet, who was lecturer in residence at the time, the symposium was concerned with selected areas of immunology and virology.

For the most part these papers are very good reviews. They include enough background information so that the reader who is only casually acquainted with the specific topic under discussion can understand the significance of the new advances in knowledge. Although they are primarily discussing basic research, the authors consistently attempt to explain how fundamental discoveries in their area have important medical implications. Indeed, some of the conjectures are highly provocative.

The authors are so well-known that mention of their names will suffice to indicate the subject. A partial list includes Burnet, Haurowitz, Pappenheimer, Billingham, Dan Campbell, Wedgewood, W. Barry Wood, Luria and Albert Sabin.

No reader is likely to have keen interest in all of the papers, but he will find them unusually well written and packed with factual information. Unfortunately the written symposium does not contain any of the discussions that occurred at the meeting itself. Nevertheless this is a valuable reference volume, for researchers and students in immunology and virology. The book is made of a good grade of paper and strongly bound. A brief but helpful index is included. E.S.

YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY. Edited by WILLIAM B. WARTMAN, B.S., M.D. Pp. 502; 138 ills. Chicago: The Year Book Publishers, Inc., 1959. Price, $8.50.

THIS volume consists of abstracts of papers on pathology and clinical pathology which appeared during the period covered by the "series year." As before, the editor has performed a valuable service with careful selection, competent review, and oftentimes accompanying editorial comment on the articles abstracted. In addition, he has included three "off-beat" articles which the reader will find most interesting. These are: "A Century of Cellular Pathology," by Sir Roy Cameron; "The Individual Basis of Biologic Variability in Cancer," by Ian Macdonald; and "Diseases Terminating in Dropsical Effusion," A prospect of Richard Bright on the Centenary of his death, by Robert Kark.

Pathologists and clinical pathologists will welcome this volume as they have its predecessors in this series. C.Z.

HUMAN NEUROANATOMY. BY RAYMOND C. TRUEX, Professor of Anatomy, Hahnemann Medical College. 4th ed. Pp. 511; 363 ills. Baltimore: The Williams & Wilkins Company, 1959. Price, $10.00.

IN their preface to the first edition, Strong and Elwyn state that they attempted to link structure and function into a dynamic pattern without sacrificing anatomical detail.

The present edition edited by Professor Truex follows the concepts of the original authors. Major changes were made in Chapters 1 and 13 and minor revisions in the remaining chapters. One new chapter has been added on the gross aspects of the brain and spinal cord and a superb one on the blood supply of the central nervous system.

The book is divided into 21 chapters. The first part dealing mainly with general organization and meaning of the nervous system, its embryology and histological structure and with some fundamental neurological problems applied to man. The second portion is devoted to the architectonics of the central nervous system.

Dr. Truex has added 37 new illustrations to the text, 23 in color. Many highly schematic and enlarged diagrams of major nervous pathways were designed to provide visual continuity to different levels of the central and peripheral nervous system.

This volume is a classic on human neuroanatomy and should be valuable to the student as well as general practitioner or specialist interested in this subject. M.S.

ENZYMOPATHOLOGIE: ENZYME IN KLINIK UND FORSCHUNG. By ROLAND RICHTERICH, Medizinische Universitätsklinik, Basel. Pp. 703; 132 ills. Berlin–Göttingen–Heidelberg: Springer-Verlag, 1958. Price, DM 128.

THIS volume is a highly systematized assemblage of information and concepts in both basic and clinical enzymology. Not a mere catalog, it has the virtues of continuity, clarity and of being presented in an interesting and stimulating manner. It is up-to-date at least through 1956, containing excellent discussions for instance of transaminase, but occasionally surprising omissions such as the mode of action of epinephrine on phosphorylase. The volume is divided into three sections: first, a brief but authoritative account of enzymes and their reactions and their relationships to morphology and function; second, general "enzymo-pathology," a discussion of "in-born errors," tumors, and the like; and third, special or organ "enzymo-pathology." On the whole the author does a heroic job of bringing together data which are widely scattered in experimental and clinical literature, and uniting them in a meaningful way. The documentation is excellent and representative. The tables of data concerning enzymatic activities in various tissues in different physiological and pathological situations are invaluable; the diagrams of integrated metabolic schemes are less impressive. One wonders, however, why the author overemphasizes certain topics, for example, the detailed consideration of the therapeutic use of cytochrome c. The volume nevertheless approaches its goal of offering both the clinician and clinical investigator a sound and comprehensive survey, and implicitly sets up many guiding concepts for the thoughtful reader. The encyclopedic, though integrated, nature of this book, re-inforced with sound critical judgment, recommends it as a most useful source book of fact and principle.

S.S.

THE MAST CELLS. By JAMES F. RILEY, M.B., CH.B.(HONS.), M.D., PH.D., Consultant Radiotherapist, Royal Infirmary, Dundee. Pp. 182; 65 ills. Edinburgh and London: E. & S. Livingstone Ltd., 1959 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $6.75.

THIS is a timely monograph on "mast cells" which have acquired renewed and intense interest in recent years. The author moreover, is admirably qualified to present a critical summary of information regarding these remarkable cells. The material is divided into two major sections. The first is a review of the literature, mainly up to 1950 when the work described in the second part began. The second part consists largely of the author's Ph.D. thesis, "Functions of the Tissue Mast Cells," written in 1958.

All aspects of mast cells are comprehensively discussed, including their relationship to heparin and histamine, the effects of histamine liberators, and so forth. A general discussion on the functions of tissue mast cells completes the text.

This volume is recommended to all who are concerned with the functional role of mast cells in a wide range of physiological and pathological reactions. C.Z.

EISENSTOFFWECHSEL. Edited by PROF. DR. W. KEIDERLING, Freiburg. Pp. 298; 138 ills., some in color. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $11.40.

THIS excellent book was written to honor Ludwig Heilmeyer on his 60th birthday. It contains contributions by 30 authors of Europe and America including M. Bessis of Paris, C. V. Moore of St. Louis, E. Undritz of Basel and J. Waldenström of Lund. The articles are written in English, French and German. They pertain to methods, functions of iron compounds, and the physiology, pathology and therapy of iron metabolism. The book is richly illustrated and well supplied with references. The summary of the articles represents a comprehensive review of our present knowledge of research and clinic of iron metabolism. The book is highly recommended to all physicians who are interested in this field. W.E.

DIE GRUNDLAGEN DER EIERSCHALENTHERAPIE. By PROF. DR. STEFAN KROMPECHER, University of Debrecen, Hungary. Pp. 83; 50 ills. Jena: Gustav Fischer Verlag, 1958. Price, DM 11.

THE author concludes from animal and clinical studies that the daily administration of 3 gm. of sterilized ground chicken shell is of value in the treatment of both rickets and anemia in infants. As egg shell contains calcium and phosphorus and according to the author some vitamin D_3, an anti-rachitic effect appears reasonable though the animal experiments leading to this conclusion are

poorly controlled. The hematopoietic effect is not due to iron as egg shell supplies insignificant amounts of this element. Krompecher believes the hematopoietic effect to be indirect, a result of improvement in bone structure. N.B.

HEMATOPOIETIC MECHANISMS. Ann. New York Acad. Sci., Vol. 77, Art. 3. BY ALBERT S. GORDON AND WALTER S. ROOT AND 65 OTHERS. Pp. 413; illustrated. New York: New York Academy of Sciences, 1959. Price, $5.00.

THIS volume contains the papers which were presented at a conference on Hematopoietic Mechanisms, held by the New York Academy of Sciences on May 1 and 2, 1958. The material is grouped into four major sections: 1) Techniques Used in the Quantitative Study of Blood Cells; 2) Hormone Control of Blood Cell Formation; 3) Hemopoietin; and 4) Life Span of Blood Cells.

The articles are well written by competent investigators and contain much information of current interest. The volume is recommended to physiologists and internists as well as to others who are interested in this rapidly advancing field. C.Z.

PSYCHOANALYSIS SCIENTIFIC METHOD AND PHILOSOPHY. Edited by SIDNEY HOOK, New York University. Pp. 370. New York: New York University Press, 1959. Price, $5.00.

A DISTINGUISHED group of psychoanalysts met with a distinguished group of philosophers of science in a free, critical interchange of views on the scientific status of psychoanalysis. The result is an interesting and readable contribution on psychoanalysis as a scientific theory.

On reading this book, this reviewer becomes more convinced of the veracity of the remarks made by Dr. Heinz Hartmann; namely that the task of defining psychoanalytic concepts, and the achievement of a higher level of clarification and systematization of psychoanalytic hypotheses, rests, in the main, still with the analyst.

This book should be of great interest to everyone interested in the theory of human behavior. M.B.

FUNDAMENTALS OF OTOLARYNGOLOGY. BY LAWRENCE R. BOIES, M.D., Professor and Chairman Department of Otolaryngology, University of Minnesota Medical School, AND 7 ASSOCIATES. 3rd ed. Pp. 510; 212 ills. Philadelphia: W. B. Saunders Company, 1959. Price, $8.00.

THE new edition of this standard textbook, designed to present fundamental information to the undergraduate medical student or to the physician who is not a specialist in otolaryngology, has been completely revised to include new technical procedures and new therapeutic agents. While the format of the book is essentially the same as in the preceding editions, four new chapters have been added to cover reconstructive nasal surgery, maxillofacial surgery, tumefactions of the neck and disorders of the salivary glands. The emphasis on diagnosis and treatment of the commonly encountered problems in otology, rhinology, laryngology and bronchoesophagology deserves special commendation. The success and popularity of the work are attested not only by three editions since it was first published in 1949, but also by the Spanish and Italian editions. H.S.

STEROIDS. BY LOUIS F. FIESER, Sheldon Emery Professor of Organic Chemistry, and MARY FIESER, Research Fellow in Chemistry, Harvard University. Pp. 945; illustrated. New York: Reinhold Publishing Corporation, 1959. Price, $18.00.

THIS volume is a completely revised account of the whole field of steroid chemistry and, in fact, replaces the well-known text, "Natural Products Related to Phenanthrene" (3rd ed., 1949). The authors have organized the material on steroids into a series of topics, each of which is reasonably complete in itself. The early work on a given subject is presented as background for consideration of subsequent developments, often including work of very recent publication. In this new and readable format, one finds expertly informative chapters on cholesterol, vitamin D, ketones, sterols, bile acids, estrogens, androgens, progestogens, adrenocortical hormones, cardiac-active principles, sapogenins, alkaloids, and many related substances. Biochemists will find this book a highly desirable reference text. In addition, it contains much basic information of interest to clinical investigators who are working in relevant areas. C.Z.

HEADACHE: DIAGNOSIS AND TREATMENT. Edited by ARNOLD P. FRIEDMAN, M.D., Department of Neurology, Columbia University and H. HOUSTON MERRITT, M.D., Department of Neurology, Columbia University.

Pp. 401; 24 ills. Philadelphia: F. A. Davis Co., 1959. Price, $8.00.

This book, written by twelve authors, has thirteen chapters which deal with diagnosis, and the medical and surgical treatment of headache, and covers the topic thoroughly. There is some repetition in the text which the editors thought desirable in order to permit the various contributors to express their viewpoints with regard to problems which are still controversial. This may detract from the effectiveness of the book for the general practitioner, who might prefer a definite statement as a guide in diagnosis and treatment, rather than conflicting views.

The varying viewpoints of the contributors may be somewhat confusing to the practicing physician for whom it is stated the book was written. As an example, Temporal Arteritis is discussed in two sections; one section mentions visual loss as a complication, while the other makes no mention of this serious and not infrequent complication.

One section, of 47 pages, deals with the surgical treatment of the major cranial neuralgias, with illustrations of the anatomic relationship of the various cranial nerves and considerable description on surgical techniques. Although much of this information would not appear to be of interest to practicing physicians who see the great majority of headache problems, the book otherwise should be a helpful reference. I.G.

The Clinical Examination of the Nervous System. By G. H. Monrad-Krohn, M.D., F.R.C.P., Professor Emeritus of Medicine (Neurology), University of Oslo, with the assistance of Sigvald Refsum. 11th ed. Pp. 466; 173 ills. New York: Paul B. Hoeber, Inc., 1958. Price, $9.50.

This old standard which is one of the books of the neurologist's bible has been known to this reviewer for many more years than this neurological life-time. It came to the writer's notice in his father's library. There it was a highly valued, although smaller book, in an earlier edition.

It is too well known and established to need any detailed mention of its contents. It is second to none in its field and for every neurologist or other physician who wrestles with the problem of neurologic diagnosis it is a must and it should be easily available. It has settled many an argument and enlightened many a discussion.

It is interesting to this reviewer that this able clinician, as have others, emphasizes the value of the clinical examination and observation, not to mention the careful history. This is true even though they are often very time-consuming. Ancillary aids cannot replace direct clinical observation.

As before there are chapters on aphasia examination, interpretation of roentgenograms including angiograms, the electro-encephalogram and electromyograph which are especially recommended to all serious students of the science of neurology.

Considering the increasing importance which neurology is assuming in medicine today, this book should be in every physician's library. S.G.

Transactions of the Third Conference on Glaucoma. Edited by Frank W. Newell, M.D., University of Chicago. Pp. 245; 75 ills. New York: Josiah Macy, Jr. Foundation. 1959. Price, $5.25.

This is another Josiah Macy, Jr. Foundation Conference. There are 24 contributors who participate in the four phased discussion.

The timely subject of Tonography is discussed in great detail and an effort is made to evaluate this clinical test in the diagnosis and management of glaucoma. The authors try to determine which types of case can be more definitely classified by the proper interpretation of the tonographic findings.

The two other topics discussed are in close relationship to the above; namely Consensual Changes in Intraocular Pressure and Osmotic Factors in the Formation of Aqueous Humor.

The authors are recognized authorities in their field and discuss these subjects at great length and with informality and candor.

For anyone doing tonography this publication will be a source of information and personal satisfaction. L.H.

Progress in Hematology, Vol. II. Edited by Leandro M. Tocantins, M.D. with 19 contributors. Pp. 290; 45 ills. New York: Grune & Stratton, Inc., 1959. Price, $9.75.

This is the second in a series of books devoted to survey reviews of advances in important areas of hematology. Among the topics discussed in the present volume are: Dynamic Cytology; Recovery from Radiation Injury with Special Consideration of the Use of Bone Marrow Transplantation; Physical and Chemical Factors in the Sickling Phenomenon; Humoral Factors in Erythropoiesis; Kernicterus; Hemolytic Disease of the Newborn Due to ABO Incompatibility; Transmis-

sion of Leukemia; Hematologic Aspects of Serotonin; Chemotherapy of Chronic Myeloid Leukemia; and Lipid Anticoagulants.

The contributors are well-qualified workers in their respective fields. Internists in general, and hematologists in particular, will find much of interest in this volume.

C.Z.

ON THE MYSTERIOUS LEAP FROM THE MIND TO THE BODY. A WORKSHOP STUDY ON THE THEORY OF CONVERSION. Edited by FELIX DEUTSCH, M.D., Boston Psychoanalytic Institute. Pp. 273. New York: International Universities Press, 1959. Price, $5.00.

THE contributors to this volume were participants, over a several-year period, in a workshop on psychosomatic problems held under auspices of the Boston Psychoanalytic Society and led by an eminent pioneer in the psychosomatic field, Dr. Felix Deutsch. A third of the chapters are by Dr. Deutsch himself; the influence of his clinical perspicacity and theoretic sophistication is apparent in most of the rest. The dominant theme of the volume is to place the conversion process in its proper context, that of the always on-going interaction of somatic processes with psychic ones, and to demonstrate the ego's way of attempting to repair early object loss by symbolizing the lost object in a body organ. The rich and thought-provoking contents of this volume will probably be more readily appreciated by psychiatrists and physicians already possessed of some acquaintance with psychoanalytic literature.

M.B.

REGULATION OF CELL METABOLISM. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and CECILIA M. O'CONNOR, B.Sc. Pp. 387; 109 ills. Boston: Little, Brown & Co., 1959. Price, $9.50.

THE latest research findings concerning regulation of cellular metabolism were presented and discussed at a Ciba Symposium held in July, 1958. The proceedings of that meeting were recorded and made available in this volume which is perhaps the first survey of a variety of aspects of the nonhormonal regulation of cellular metabolism. It will be of interest to all who are involved in basic research at cellular and subcellular levels.

C.Z.

A WAY OF LIFE AND SELECTED WRITINGS OF SIR WILLIAM OSLER. Edited as a Centenary Tribute by a Committee of the Osler Club of London, with the help of W. W. FRANCIS, M.D. Pp. 278; 5 ills. New York: Dover Publications, Inc., 1959. Price, $1.50.

THROUGH a special arrangement with the Oxford University Press, its 1951 volume, *Selected Writings of Sir William Osler*, is now made available in a paperback edition by Dover Publications of New York. Reprinted from the British text with a new title, *A Way of Life and Selected Writings of Sir William Osler*, it provides an easily available collection of this great physician's writing at a low price. This service is a welcome one for students in the health professions, professional and general readers.

Although Sir William Osler died in 1919, his hold on the memories of many senior medical men still testifies to the rare and personal quality of his leadership. This reviewer often heard his physician-father speak of Dr. Osler and read the well known textbook when first interested in studying medicine. Osler greatly stimulated the intellectual life of medicine in his day. Through a fine biography by Dr. Harvey Cushing and recent reprintings of Osler's work, such as the present paperback, one can recapture the knowledge, philosophy and wisdom of this outstanding man.

In an introduction to this book, Sir Geoffrey Keynes, the eminent British surgeon, writes: "The generation that knew Osler is quickly passing, and with it must pass the memory of his living presence. His text-book of Medicine, although it can remain a pattern of style in medical writing, like every other text-book, cannot, with the advances of the Art and Science, be for long an active influence. Osler's memory cannot, indeed, be served better than by reading, or a re-reading of his addresses and essays." This selection of favorite and lesser known writings will help make Osler's influence a lasting one.

The committee of physicians which edited this collection of biographical, historical and inspirational articles did not aim to present their patron saint as a pathologist or clinician, but to depict him as speaker and essayist telling of his concern with the history of medicine and of medical men and of his love of books. The first essay, "Creators, Transmuters, and Transmitters," written for a Shakespeare exhibition in 1916, is hard to come by, and Osler's three letters to his house physicians describing his visits to continental hospitals and towns in 1890 are collected for the first time. "A Way of Life," and, "A Student Life," are his best known

addresses; essays on Sir Thomas Browne and Robert Burton tell of two English writers who were Osler's special heroes, and the masterly papers about Michael Servetus—victim of religious bigotry—and William Beaumont, A Backwood Physiologist, document a charming prose style.

Other gems among the sixteen essays in this collection are: "Books and Men," "The Old Humanities and the New Science," "Teaching and Thinking," "The Growth of Truth as Illustrated in the Discovery of the Circulation of the Blood," "Gui Patin," "The Young Laennec," "Illustrations of a Bookworm" (genus *Anobium*), and, "The Collecting of a Library." While one cannot find some personal favorites such as, "Aequanimitas," and "An Alabama Student," this book includes a fine sample of Osler's essays in its 278 pages.

Osler in a paperback edition is a publishing event, making more widely available the wisdom from his pen. Here the reader can find an inspiration for the classics, a feeling for the humanities and the beauty of literature, and the connections between science, philosophy and history. This durable, yet inexpensive, volume has a good chance to get to those for whom it is intended. Here for all readers are masterpieces that will continue to inspire. F.R.

A Primer of Water, Electrolyte and Acid-Base Syndromes. By E. Goldberger, Lecturer in Medicine, Columbia University. Pp. 322; 37 ills. Philadelphia: Lea & Febiger, 1959. Price, $6.00.

The subject of this text has gained wide prominence in recent years with improved methodology and extensive application of biochemical advances to the clinical aspects of fluid and electrolyte disturbances and their correction. The dissemination of this knowledge is an important function which is lucidly and concisely achieved in this monograph. The conventional interpretation of body water, electrolyte distribution and osmotic pressure relationships introduces the discussion together with descriptions of humoral factors operating in their control. The following sections deal with syndromes associated with water, electrolyte and acid-base disturbances. The format used in presenting the conditions, such as water loss, sodium loss, acidosis, alkalosis and many others, is useful in promoting a clear understanding of the pathophysiology, etiology, clinical manifestations, laboratory correlations, and treatment of the respective disorders. Sections on fluid therapy in surgical and pediatric patients have been abbreviated to a point which limits their usefulness. The text is concluded with a discussion of solutions available for fluid therapy and their routine indications. This combined clinical and biochemical approach to the subject of fluid and electrolyte management provides an excellent reference for students and physicians interested in these problems. C.S.

The Central Nervous System and Behavior. Edited by Mary A. B. Brazier, Ph.D., Neurophysiological Laboratory, Massachusetts General Hospital, Boston. Pp. 450; 168 ills. New York and Washington, D.C.: Josiah Macy, Jr. Foundation and The National Science Foundation, 1959. Price, $5.25.

This Macy Conference had several objectives, one of which was to familiarize scientists of Western Countries with Russian work on the central nervous system and behavior. Accordingly, the major portion of this volume consists of surveys of developments in this area by Soviet investigators. The titles of the major sections will indicate the scientists and the nature of the work covered: "Russian Contributions to an Understanding of the Central Nervous System and Behavior—A Pictorial Survey;" "The Nineteenth Century Background of the Russian Neurophysiologists, and Sechenov;" "Danilevsky, Wedensky, and Ukhtomsky;" "Pavlov;" "Bechterev;" and "Post-Pavlovian Development in Conditioned Reflexes."

In addition to the foregoing, other presentations included in this volume are: "Brain Stimulation and Conditional Reflexes;" "Electroencephalographic Studies of Conditioned Learning;" and "Electrical Correlates of Conditioned Learning."

The transactions of the entire meeting, discussions as well as the original papers, make worthwhile reading. Moreover, one may gain at the same time an excellent perspective of the Russian contributions to studies of the central nervous system and behavior. C.Z.

Lehrbuch der Geburtshilfe. By Prof. Dr. Heinrich Martius. 4th ed. Pp. 731; 767 ills., many in color. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $14.20.

In this fourth edition, which was revised with the help of H. Hartl and K. Droysen, the high standards of the previous editions are maintained and as a result it is one of the best obstetric texts available today. The senior author is an experienced and able teacher and clinician who was director of the Göttingen Frauenklinik for 25 years before his recent retirement. Much of the statistical material in this book is derived from his work in that clinic.

The authors have attempted to prepare a book which would serve as a student text and at the same time as a reference for practicing physicians. In the most part this aim is well accomplished, because while a considerable amount of theoretical material is presented precise methods for managing normal pregnancy and delivery as well as the complications are given in detail.

The illustrations are excellent and well placed in relation to the textual material. For the most part they are halftones and line sketches and many are in color. Unfortunately, there is no formal bibliography, most of the references are included in the text and usually only the authors' names are mentioned.

The material is arranged in a standard manner, namely, pelvic anatomy and physiology, the physiology of pregnancy and of the fetus, normal and abnormal pregnancy, and normal and abnormal labor and delivery. In each of these sections the normal physiologic mechanisms as well as the abnormalities are discussed in detail. The section of the newborn is excellent and includes normal physiologic reactions as well as both common and rare diseases. The latter includes sections on birth injury, abnormalities related to environmental adaptation, infection and prematurity.

Problems such as hypofibrinogenemia, marginal sinus rupture, amniotic fluid infusion, hemolytic disease in the newborn, maternal diabetes, and others are well covered.

In general the authors have been quite successful in preparing a text to serve the purposes of both medical students and practitioners. While some of the methods of treatment differ from ours and might not be applicable in many instances, the large amount of material related to normal and abnormal pregnancy changes makes this an outstanding reference book. J.W.

MOLOY'S EVALUATION OF THE PELVIS IN OBSTETRICS. By CHARLES M. STEER, M.D., Associate Professor of Clinical Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University and the Sloane Hospital for Women. 2nd ed. Pp. 131; 57 ills. Philadelphia: W. B. Saunders Co., 1959. Price, $4.00.

THE second edition of Moloy's Evaluation of the Pelvis in Obstetrics has been prepared by Charles Steer who not only has long been interested in the problem of cephalo-pelvic disproportion but who has worked with the original author. As is indicated in the preface the book does not replace standard obstetric texts but simply expands upon the effects of pelvic shape upon the mechanism and outcome of labor, the methods for detecting abnormal pelves and for determining their adequacy and the manner in which problems of disproportion can be solved.

The material is divided into 5 sections, the first of which is devoted to the general morphology of the pelvis. In Section II the clinical evaluation of the female pelvis is clearly described and amply illustrated. The mechanism of labor as influenced by the shape of the bony pelvis is presented in the next section and the last two are devoted to lucid and detailed discussions of the management of arrested labor and the recognition of disproportion. Various methods for measuring the pelvis precisely are described and that of Caldwell and Moloy is presented in detail.

In contrast to the practice of some obstetricians who have ordered Roentgen-ray pelvimetry almost routinely, Steer relies upon clinical examination primarily and reserves Roentgen study for selected patients in whom cephalopelvic disproportion appears to be interfering with the progress of labor. He estimates this to be necessary in about 10%.

This book, though small, covers the subject of pelvic evaluation and the reasons for and management of disproportion and abnormal labor clearly and completely. It should prove to be a valuable addition to the libraries of medical students as well as those who practice obstetrics and it could be read to great advantage by radiologists. J.W.

ADVANCES IN PROTEIN CHEMISTRY, VOL. XIII. Edited by C. B. ANFINSEN, JR., M. L. ANSON, KENNETH BAILEY AND JOHN T. EDSALL. Pp. 525; illustrated. New York: Academic Press Inc., 1958. Price, $13.80.

THE present volume differs from its predecessor in this series in that, because of length, only four reviews are presented. These are: The Use of Immunochemical Analysis in

Studies on Proteins, by P. Grabar; Protein-Carbohydrate Complexes, by F. R. Bettelheim-Jevons; The Silk Fibroins, by F. Lucas, J. T. B. Shaw, and S. G. Smith; and Synthesis and Chemical Properties of Poly-α-Amino Acids, by E. Katchalski and M. Sela.

All of the surveys are critical and authoritative as each contributor has intimate personal knowledge of the field he discusses. This should be a valuable reference volume for workers in these and related areas.

C.Z.

CLINICAL DERMATOLOGY FOR STUDENTS AND PRACTITIONERS. By HARRY M. ROBINSON, JR., AND RAYMOND C. V. ROBINSON, University of Maryland School of Medicine. Pp. 242; 116 ills. Baltimore: The Williams & Wilkins Company, 1959. Price, $8.50.

THE ROBINSONS have produced a text on dermatology which has the purpose of carrying on the tradition of morphologic dermatology as it was taught effectively at the University of Maryland School of Medicine for many years under the supervision of the authors' father, Dr. Harry M. Robinson, Sr. This book presents mainly in outline form certain general considerations of the anatomy, physiology, pathology and etiologic factors in skin disease, plus treatment. The bulk of the volume, however, deals with morphologic dermatology and includes a number of sub-headings: Regional involvement by common dermatoses; numerous differential diagnosis charts; certain lists of conditions and a number of specific eruptions of particular lesion type, macular, papular, and others; also eruptions of specific structures, such as sweat glands; nails and peripheral vascular diseases are included. There is a section on tropical diseases. The material is well indexed.

The Reviewer feels that the outstanding feature of this book is the illustrations. These illustrations, in black and white, with the text, form a good compendium for students and practitioners but are too elementary for the individual specially interested in dermatology.

H.B.

IMMUNOPATHOLOGY, 1ST INTERNATIONAL SYMPOSIUM. Edited with 51 contributors by PROF. DR. PIERRE GRABAR (Paris), and DR. PETER MIESCHER (Basel). Pp. 520; illustrated. Basel: Benno Schwab & Co., 1959 (Intercontinental Medical Book Co., New York, U.S. Agents). Price, $16.25.

THIS volume represents the proceedings of the first International Symposium on Immunopathology held in Basel, Switzerland. Fifty-one participants present papers and enter into discussion of the work described. These scientists include many of the outstanding immunologists and pathologists of Europe and America. The purpose of the meeting was to present the work and to allow free discussion with the view of increasing understanding of this new and complex and rather rapidly expanding field. This purpose is admirably served and the book itself serves as an excellent collection of otherwise widely scattered information in immunologic diseases.

The book is divided into six sections, each concerned with a specific aspect of immunopathology. They are: I. General immunopathology; II. The properdin system and its significance in immunopathology; III. Agammaglobulinemia and antibody deficiency syndromes; IV. Organ-specific immunopathology, including the nephritis problem, the liver, spermatozoan antibodies, thyroiditis, and homograft immunology; V. Inflammatory immunoreactions, including the physiopathology of the inflammatory reaction in general, allergic reactions, the pathogenic significance of antigen antibody complexes, and the Schwartzman phenomenon; VI. Rheumatoid arthritis and disseminated lupus erythematosus, including the rheumatoid factor, the L.E. factor and the interrelationships between these two diseases.

The book is printed in English, French, and German with more than half the articles in English and with English, French, and German summaries after each section.

This is most interesting material ably presented by many of the scientists who are developing this newer area of medicine. The book is highly recommended for those whose interest or work is in the broad fields of immunology, pathology, or connective tissue diseases.

H.W.

VIRUS GROWTH AND VARIATION. Edited by A. ISAACS AND B. W. LACEY. Pp. 272; 33 ills. and 1 color plate. New York: Cambridge University Press, 1959. Price, $7.00.

THIS Symposium, the ninth of the Society for General Microbiology, was held in London, in April, 1959. As in the earlier "Symposium on Virus Multiplication," an impressive and authoritative series of papers were presented. Among the topics considered were: Viruses: a Survey of some Current Problems; Growth of Bacteriophage; Some Observations concerning the Reproduction of RNA-containing Animal Viruses; Viral Interference; Growth Studies with Herpes Virus; Studies

on Vaccinia Virus in HeLa Cells; The Chemical Approach to the Study of Animal Virus Growth; Fluorescence Microscopy; Observations of Virus Growth with Aminoacridines; and Electron-Microscopic Observations on Adenoviruses and Viruses of the Influenza Group.

Several of the articles are beautifully illustrated.

Biologists, geneticists, biochemists, and microbiologists will find these presentations informative and stimulating. C.Z.

MEDICINE AND ANTHROPOLOGY. Edited by IAGO GALDSTON, M.D. Pp. 165; 26 ills. New York: International Universities Press, Inc., 1959. Price, $3.00.

THIS volume, a valuable addition to the "March of Medicine" series of The New York Academy of Medicine, contains six public lectures on medicine and anthropology. Two of the contributors are physicians: Dr. Paul Fejos, of the Wenner-Gren Foundation, also an anthropologist, and Dr. Alexander Leighton, Professor of Sociology at Cornell University. The former discusses, "Man, Magic and Medicine," and the latter, "Mental Illness and Acculturation." Other distinguished professors also contribute readable, interesting and thought-provoking essays: John Dodds of Stanford University on, "The Humanist Looks at the Doctor;" Marston Bates (Zoology, Michigan), "The Ecology of Health;" F. S. C. Northrop (Philosophy and Law, Yale), "Cultural Mentalities and Medical Science;" and, Raymond Firth (Anthropology, London), "Acculturation in Relation to Concepts of Health and Disease." Dr. Iago Galdston of The New York Academy of Medicine, editor of the volume, adds an introduction to the series. The book is technically attractive and contains pertinent illustrations and references.

These authors emphasize the fact that man is a culture-bearing animal, culture being the socially inherited characteristics of society. Both professional and folk medicine operate in a social setting and are, therefore, closely related to cultural phenomena, an important concept in the acceptance or rejection of health measures in any part of the world. Our complex American culture, and the many problems posed today by its diverse origins, testify to the need for understanding of the individual and the group, culturally, socio-economically and physically. Studies in anthropology, psychiatry, and sociology—such as those cited in the above lectures—will bring new insights and advances in the health needs of people. This book is highly recommended for the interested reader. F.R.

ANTIBIOTICS ANNUAL, 1958–1959. Edited by HENRY WELCH, PH.D., AND FELIX MARTI-IBANEZ, M.D. Pp. 1107; illustrated. New York: Medical Encyclopedia, Inc., 1959. Price, $12.00.

THIS volume contains the proceedings of the Sixth Annual Symposium on Antibiotics which was held in Washington, D.C., in October, 1958. A large number of papers, both from foreign countries and the United States, and dealing specifically with a wide variety of antibiotics and chemotherapeutic agents, make up the bulk of the text. In addition, and most interesting and informative, are the following general papers: The First Thirty Years, by F. Marti-Ibañez; Penicillin in Perspective, by H. W. Florey; Antibiotics of Actinomycetes, An Introduction and An Outlook, by S. A. Waksman; The Impact of Antibiotics on American Medicine, by C. S. Keefer; and History of the Broad-Spectrum Antibiotics, by H. F. Dowling.

Clinicians and microbiologists will find this a useful reference book. C.Z.

GYNECOLOGIC ENDOCRINOLOGY. BY GARDNER M. RILEY, PH.D., University of Michigan Medical School. Pp. 330; 67 ills. New York: Paul B. Hoeber, Inc., 1959. Price, $8.50.

BOOKS on endocrinology often are not particularly helpful to the clinician and may even be confusing and frustrating because they present a profusion of theory and the results of animal experimentation, but devote little space to what actually happens in the human being. *Gynecologic Endocrinology* however is quite different; the material is presented in an interesting, lucid style, it contains much practical clinical material but the fundamental physiologic mechanism upon which diagnostic methods and treatment are based are also clearly described. The author, an experienced endocrinologist, has been closely associated with and has a clear understanding of clinical problems.

In the first section, Endocrine Physiology, the female endocrine glands and their complicated inter-relationship with other glands, the breast and the endocrinology of pregnancy are discussed.

Section two is devoted to the clinical aspects of female endocrinology from birth

until senescence. It includes discussions of the diagnosis and management of a variety of conditions such as abnormal bleeding, infertility, pregnancy, abnormal sexual development and various endocrine syndromes.

Section three, which is devoted to diagnostic procedures and the various endocrine preparations, contains perhaps the most interesting and useful material in the entire book. It is difficult for most clinicians to know what to expect from endocrine assay and in which patients to order such studies. Much help can be obtained from this book because for each hormonal substance the condition in which its measurement may be of importance is described. In addition the details of assay methods for each of the substances are presented.

The book is well illustrated with clinical photographs, photomicrographs, charts and tables. It should be of great help to students, family physicians, practicing internists and obstetrician-gynecologists because it provides a ready and complete reference to clinical gynecologic endocrine problems. J.W.

Information Theory in Biology. Edited by Hubert P. Yockey, Robert L. Platzman and Henry Quastler. Pp. 418; illustrated. New York: Pergamon Press, 1958. Price, $12.00.

This volume resulted from a Symposium on Information Theory in Health Physics and Radiobiology which was held in Gatlinburg, Tennessee, in October, 1956. Its common denominator was "the possibility that the life sciences could develop mathematical systems suitably their own, so that this form of research could be added to the already powerful research tools available."

The subject matter is presented in seven major sections: The first appropriately consists of a "Primer on Information Theory" followed by some introductory ideas regarding the application of information theory. Succeeding sections deal with "Storage and Transfer of Information," "Determination of Information Measures," "Destruction of Information by Ionizing Radiation," "Aging and Radiation Damage," "Information Networks," and "The Status of Information Theory in Biology."

Many readers will find themselves on unfamiliar ground; nevertheless, they will gain insight into an important movement which it is hoped will lead to mathematical methods adequate for the needs of biology. Research workers in the basic biologic and physical sciences would do well to familiarize themselves with the concept elaborated in this book. C.Z.

Progress in Medical Virology, Volume 1. Edited by E. Berger, Basel, and J. L. Melnick, Houston, Texas. Pp. 304; 54 ills. New York: Hafner Publishing Co., Inc., 1958. Price, $11.50.

This is the first volume of a new international series designed to make available annual surveys in virology. It is planned to cover etiologic, diagnostic, and epidemiologic as well as the basic laboratory aspects of virology. Indeed, the initial volume has successfully achieved these broad aims as may be judged from the following titles: Nucleic Acid as the Carrier of Viral Activity; The Significance of the Viral Carrier State in Tissue Culture Systems; Advances in the Study of the Enteroviruses; Coxsackie Virus Infections of the Newborn; Influenza, 1957, A Variant and the Pandemic; Tick-Borne Spring-Summer Encephalitis; Russian Spring Summer Virus in India, Kyasanur Forest Disease; and Direct Virus Antibody Flocculation Reactions.

All workers interested in viruses will want to have this and future volumes of the series for reference. C.Z.

The Functions of the Endocrine Glands. By Peter F. Hall, M.D., Assistant Lecturer in Physiology, University of Sydney. Pp. 290; 77 ills. Philadelphia: W. B. Saunders Company, 1959. Price, $5.75.

This excellent book fills a sorely felt need in the endocrine literature. It is directed towards the student and for this reason clinical diseases involving the endocrine system are not emphasized. Primarily it is a textbook of basic chemistry and physiology as related to endocrine function. There is an introductory chapter dealing with elementary organic chemistry in order to assist the reader who has been long removed from this subject. The various endocrine glands are considered systematically in relation to their physiology, function and the chemistry and action of their hormones. There are also chapters on Endocrine Factors in Growth, Maturation, and Decline, The Nervous Control of the Endocrine Glands and a chapter on Steroid Metabolism.

The text is written clearly and in an elementary fashion and should make this difficult subject understandable, even to the reader whose background in chemistry and physiology is meager. It is in no way a ref-

erence text for endocrine disease but should be invaluable for the student or physician who is interested in gaining a basic understanding of endocrine function. B.C.

KLINISCHE METHODEN DER BLUTGERINNUNGSANALYSE. By PROF. DR. J. JÜRGENS, and DOZ. DR. F. K. BELLER. Pp. 408; 104 ills. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $13.35.

THIS is a comprehensive monograph on the blood clotting mechanism. Physiologic and clinical aspects are discussed in the first section, followed by a systematic consideration of the various components which enter into the clotting phenomenon. The final chapter describes reagents and methods for determining individual clotting factors.

The text is well illustrated and there is an adequate, up-to-date bibliography. It is written with the thoroughness characteristic of German workers. It may be recommended to those students of blood coagulation who read German. C.Z.

THERAPEUTIC ELECTRICITY AND ULTRAVIOLET RADIATION. Edited by SIDNEY LICHT, M.D. (Volume 4 of Physical Medicine Library). Pp. 373; 94 ills. New Haven: Elizabeth Licht, 1959. Price, $10.00.

THIS book consists of two major sections, the first part is concerned with the therapeutic use of electricity. Chapters are devoted to history, instrumentation, clinical use of electric stimulation, iontophoresis, and electrosleep therapy.

The second part deals with ultraviolet radiation, with chapters on its history, instrumentation, physiologic effects, and clinical uses.

Those who use electricity or ultraviolet radiations in clinical practice will find this a useful volume. It is also recommended to anyone interested in learning of the contemporary status of these agents in physical medicine. C.Z.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Published Monthly. Illustrated.

Subscription price: 1 year $10.00; 2 years $18.00.

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All foreign subscriptions payable in advance in United States dollars.

Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, Pa.

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